JUNE 1957
VOL. XV NO 6

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

30th Scientific Sessions of the American Heart Association
Commemorating the Tercentenary of William Harvey
Chicago, Ill., from October 25–28, 1957

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

Published by Grune & Stratton, Inc.

1 of 3 survive

Until the advent of Levophed only 1 of 20 pulseless cases of myocardial shock survived. With Levophed 1 of 3 survive.* Use Levophed first in cardiogenic shock.

with **Levophed®** bitartrate

Natural antishock pressor hormone

Every day Levophed reverses "irreversible shock."

*Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico*, 47:305, Aug., 1955.

Winthrop LABORATORIES
New York 18, N. Y.

11348

Levophed (brand of levarterenol), trademark reg. U. S. Pat. Off.

Circulation

JUNE, 1957
VOL. XV NO. 6

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Reflections on Electrocardiography

THE PHYSICIAN who purchases an electrocardiograph and expects it to write out the correct cardiac diagnosis in all patients is deluding himself, and he may become a danger to his community. Unfortunately, most patients and many physicians consider the electrocardiogram to be nearly infallible, and many people have been wrongly condemned to the life of a cardiac cripple solely on electrocardiographic evidence. These patients illustrate the seamy side of electrocardiography and indicate how a basically accurate and reliable technic may go astray.

Some years ago electrocardiographic errors might have occasionally been due to technical difficulties arising in the actual registration of the tracings. In recent years, however, improvements in the design of equipment, including the use of differential amplifiers and the practice of grounding the subject with an electrode on the right leg, have made it possible for any physician, nurse, or technician to secure records of good quality, provided a few simple instructions are followed. Today, electrocardiographic errors are usually due to inexperienced or over enthusiastic interpretation, and not to technically bad records. This statement does not mean that the technical quality of the tracings may be ignored. This is not, and never will be true, since lead wires will occasionally be mixed, and fuses, resistances, or condensers in the electrocardiograph will go bad. The experienced electrocardiographer is always alert to recognize such mishaps and is constantly trying to maintain and improve the technical quality of the records.

How may one avoid errors in the interpretation of electrocardiograms? Experience in reading tracings and knowledge of some of the basic electric phenomena going on in the heart and how various leads function are perhaps the best answers to this question. Many other factors are, however, involved. Even in a large teaching hospital there is often pressure on the individual or group interpreting electrocardiograms to read as much as possible into the reports. Such pressure may be much greater on the internist in practice. If he doesn't come through with a report that confirms Dr. X's suspicion that Mrs. Goldrocks has "myocarditis," he will soon get a reputation of not knowing much about electrocardiography. Although it may not be easy, the physician interpreting electrocardiograms should resist the tendency to over-read the records. By so doing he will not be a party to the creation of iatrogenic heart disease and will come out ahead in the long run.

A certain number of electrocardiograms show changes that justify a clinical diagnosis without any further information. For example, the majority of tracings taken on patients with acute myocardial infarction show RS-T segment, T wave, and QRS alterations that allow the electrocardiographer to make the diagnosis in question with no other data relating to the patient. Tracings may also have similar specific diagnostic value in connection with the arrhythmias and in a few other conditions like hyperkalemia and hypocalcemia. In contrast to electrocardiograms of this kind is the large group of records that are abnormal but do not point to any single cardiac condition. Included in this category are tracings suggesting right or left ventricular hypertrophy, showing bundle-branch block, and the large heterogeneous

class of electrocardiograms that show abnormal T waves. Tracings of this kind may be very helpful by limiting the number of diagnostic possibilities and also by supplying *some evidence* favoring the presence of organic heart disease in the patient. It is in connection with assistance of the latter type that the electrocardiographic "eager beavers" do most of their dirty work. They do not know that bundle-branch block, even left branch block, may occur without any significant myocardial disease and do not appreciate how frequently T wave "abnormalities" are found in the complete absence of heart disease.

Over a period of years it has been found that in most normal subjects the T waves are upright in leads I, II, and in precordial leads taken from sites over the left ventricle. If one remembers how easily the recovery process in cardiac muscle is influenced by factors such as temperature, electrolyte levels, and hyperventilation, that have nothing to do with heart disease, it is not surprising that electrocardiograms from individuals with normal hearts may show "abnormal" T waves at times. The sensible electrocardiographer appreciates these matters and never makes a diagnosis of "coronary insufficiency" or, even worse, "coronary sclerosis" on the basis of T-wave changes alone.

A few words must be said about the hyperventilation syndrome. Although this common functional difficulty has been recognized for a long time, many physicians, including some with long experience, fail to suspect the condition either as a major or complicating cause for a patient's symptoms. Several features of the syndrome serve to confuse the unwary physician. Among its protean manifestations are pain, often in the precordial area, and sensations of air hunger, which the patient often will report as true dyspnea. Although the chest pain may superficially resemble angina pectoris, *a careful history* usually makes it clear that it is quite unlike true angina. Furthermore, the frequent occurrence of numbness and tingling in the extremities and circumoral region, peculiar sensations of tenseness and increasing hyperpnea, often culminating in syncope, usually make the nature of the disturbance clear. Finally, as mentioned above, hyperventilation frequently causes RS-T segment and T-wave abnormalities. These may be either transient or chronic and are often indistinguishable from changes due to coronary artery or other types of heart disease. The existence of electrocardiographic changes with hyperventilation has been known for many years, and in 1943 Thompson[1] reviewed the previous literature and pointed out very clearly the character of the abnormalities and the importance of their recognition. A number of other papers on this subject, including several recent ones, will be found in the literature; in spite of fairly adequate discussion, however, this matter and its important implications seem to be widely ignored. The writer believes that many hundreds, and perhaps thousands, of patients are being treated today as victims of coronary disease when they actually have nothing but hyperventilation syndrome. Poor electrocardiography is, of course, only partly responsible for this situation.

Again, we may ask, how should the physician interpreting electrocardiograms report tracings showing only T-wave abnormalities in a manner that will be as helpful as possible to the clinician and yet minimize the danger of overreading the records? There is no entirely satisfactory way for meeting this situation, but we use the deliberately vague term "suggests myocardial changes" in our reports. Most physicians in our hospital have learned that this noncommittal expression means that we consider the record to be outside of the commonly accepted limits of normal but we don't know why this is true. Physicians interpreting electrocardiograms should always have at hand as much clinical data about patients on whom tracings are taken as is possible. When this information is available, the records may be interpreted in much more specific terms than when such data are lacking. The ideal situation is for the physician responsible for the patient to interpret the electrocardiogram himself, provided he is qualified to do so. The doctor who purchases an electrocardiograph and tries to interpret the tracings himself without adequate experience and training is not much worse than is the physician who sends the tracings away to some agency for interpreta-

tion, particularly if the records are sent without much clinical data.

The foregoing material refers almost entirely to clinical interpretation of electrocardiograms. This facet of electrocardiography must always be the responsibility of the physician. Many physicians, in addition to this purely clinical use of the records, have carried out important investigations that have added immeasurably to our knowledge and the usefulness of the science. One could mention dozens of individuals who have contributed in this way, but few would disagree that Sir Thomas Lewis and Doctor Frank N. Wilson were leaders of this group. It must be pointed out, however, that the first great electrocardiographer, Wilhelm Einthoven, was not a physician but a physicist, and that one of the most important contributions in recent years, the concept of the lead vector, was developed by H. C. Burger, another Dutch physicist working with J. B. vanMilaan, a physician. In this country several biophysicists and electrical engineers, including Schmitt, Frank, McFee, and Nelson have done and are doing outstanding work on electrophysiology of the heart and electrocardiographic leads. Although some of this work is rather complicated and technical in nature, many of the important ideas developed by these scientists will in time be used to improve routine diagnostic technics.

It has been assumed for many years that, during excitation of the ventricles, the accession wave spreads in a roughly radial fashion from the endocardial to the epicardial surfaces of these chambers, and interpretation of the form of the QRS complexes in direct and semidirect (precordial) leads has been based to a considerable degree on this premise. Recent studies by Prinzmetal and associates,[2] however, suggest that the subendocardial layers are excited very rapidly with no clear tendency to radial outward spread and that this type of activation occurs only in the subepicardial regions. Similar work by Durrer, vanderTweel and Blickman[3] and Sodi-Pallares and associates[4] supports this view. Investigations carried out, with a somewhat different technic, by Scher and co-workers,[5] however, are interpreted to support the original contention that activation of the ventricles occurs in a basically endocardial to epicardial direction. This matter is of great practical as well as theoretical importance. If Prinzmetal's view is correct, the subendocardial muscle will contribute nothing to the QRS complexes obtained in direct or semidirect leads and therefore even extensive infarcts in this inner region will cause no abnormalities of the QRS complexes in the leads in question. At the moment, the writer finds it hard to believe that the subendocardial muscle is so completely silent, but further work must be done to clarify this point.

Vectorcardiography is an interesting field that has been the subject of great activity in recent years. Although Doctor Wilson and the author recorded some of the first records of this kind, using the cathode-ray oscillograph nearly 20 years ago, we have never in our laboratory had a great deal of interest or enthusiasm about vectorcardiography as a practical clinical diagnostic tool. The reasons for this view have been recorded in some detail elsewhere[6] and can only be briefly outlined here.

Since vectorcardiograms are figures obtained by combining with a cathode-ray tube 2 cardiac voltages that might be recorded individually as ordinary scalar electrocardiograms, the vector figures contain no information not present in the 2 ordinary tracings. Phase differences between peaks of R waves in the scalar records, for example, are clearly shown in the vectorcardiogram, but, except for this, the latter has little advantage. The vectorcardiogram is simply a different way of displaying the data present in the 2 ordinary tracings.

If these facts are granted, it seems obvious that leads good for vectocardiography should also be good ones for scalar records. Most vectorcardiographers have never considered their choice of leads from this point of view. If 3 leads or lead systems can be devised that will yield entirely satisfactory orthogonal components (i.e., transverse, vertical, and sagittal) of cardiac electromotive forces these leads would not only be ideal for vectorcardiography but would provide a scheme by means of which most of the data now requiring at least 9 leads

could be recorded in 3 electrocardiograms. The writer believes that the lead-field concept developed by McFee and Johnston[7–9] points to methods for accomplishing this desirable end. These ideas are further discussed in a recent paper by Reynolds, Cordes, Willis, and Johnston.[10]

Electrocardiography has advanced a great deal in the past half a century, but even though technical advances in the future may simplify and improve methods for the registration of records, the human element, concerned with interpretation of records will always be with us. In this connection it is well for all of us to keep in mind a remark so often made by Doctor Wilson. "The more one learns about the fundamentals of electrocardiography the more conservative he becomes in the interpretation of tracings."

FRANKLIN D. JOHNSTON

REFERENCES

[1] THOMPSON, W. P.: The electrocardiogram in the hyperventilation syndrome. Am. Heart J. **25:** 372, 1943.

[2] PRINZMETAL, M., KENNAMER, S. R., SHAW, C. M., JR., KIMURA, N., LINDGREN, I., AND GOLDMAN, A.: Intramural depolarization potentials in myocardial infarction. Circulation **7:** 1, 1953.

[3] DURRER, D., VANDERTWEEL, L. H., AND BLICKMAN, J. R.: Spread of activation in the left ventricular wall of the dog. III. Am. Heart J. **48:** 13, 1954.

[4] SODI-PALLARES, D., BISTENI, A., MEDRANO, G. A., AND CISNEROS, F.: The activitation of the free left ventricular wall in the dog's heart. Am. Heart J. **49:** 587, 1955.

[5] SCHER, A. M., YOUNG, A. C., MALMGREN, A. I., AND PATON, R. R.: Spread of electrical activity through the wall of the ventricle. Circulation Research **1:** 539, 1953.

[6] JOHNSTON, F. D.: Vectorcardiography. J. Chron. Diseases **2:** 104, 1955.

[7] MCFEE, R., AND JOHNSTON, F. D.: Electrocardiographic leads I. Introduction. Circulation **8:** 554, 1953.

[8] — AND —: Electrocardiographic leads II. Analysis. Circulation **9:** 255, 1954.

[9] — AND —: Electrocardiographic leads III. Synthesis. Circulation **9:** 868, 1954.

[10] REYNOLDS, E. W., JR., CORDES, J. F., WILLIS, P. W., III, AND JOHNSTON, F. D.: The use of the lead-field concept in the development of leads satisfactory for vectorcardiography. I. The sagittal lead. Circulation **14:** 48, 1956.

Medical Eponyms

By ROBERT W. BUCK, M.D.

Valsalva Maneuver. This maneuver was described by Antonio Maria Valsalva (1666–1723) in his *Treatise on the Human Ear* (*De Aure Humana Tractatus*), Utrecht, 1717. The following quotation is taken from the edition published at Leyden in 1735, chapter 5, 8, page 84.

"If a person who has a continuously discharging abscess in or near the eardrum will attempt, with his mouth and nostrils closed, to compress the air inside, then, as this is done, the bloody matter will usually flow out freely into the auditory meatus."

Serum Lipoprotein and Cholesterol Concentrations

Comparison of Rural Costa Rican, Guatemalan, and United States Populations

By NEVIN S. SCRIMSHAW, PH.D., M.D., MARTHA TRULSON, D.SC., CARLOS TEJADA, M.D., D. MARK HEGSTED, PH.D., AND FREDRICK J. STARE, M.D.

A previous study indicated that Guatemalan Indians, both male and female, tended to maintain low levels of serum cholesterol throughout adulthood but that beta-lipoprotein fractions increased with age, as is usually the case in populations in the United States. To investigate whether race was of importance in this unexpected dissociation between these lipid fractions, a similar study was done with a rural group in Costa Rica, which was comparable in the diet consumed and in many other environmental factors, but of pure European origin. At all ages the cholesterol values were slightly higher but the same type of dissociation was observed.

IN A previous report Mann, Munoz, and Scrimshaw[1] demonstrated that rural Guatemalans, subsisting on a diet low in both animal protein and calories from fat, had much lower serum cholesterol values than men and women from business and professional families living in urban areas in either Guatemala or the United States. The rural Guatemalans also showed β-lipoprotein fractions that were within the same levels for males, and higher levels for females, than upper income populations in urban Guatemala and the United States. This dissociation between serum cholesterol and certain β-lipoprotein fractions was quite unexpected and contrary to the findings of studies dealing exclusively with United States subjects.

These observations have important implications because autopsy findings indicate that the rural Guatemalan group has a much lower incidence of the complications of atherosclerosis than persons in the United States.[2] Similarly, clinical records show coronary heart disease to be common among business and professional persons in urban areas in both the United States and Guatemala and exceedingly rare among lower income persons residing in rural Guatemala.

These results suggested that environmental differences, among which diet might be the most important determining factor, were responsible for the relative freedom from coronary heart disease and other complications of atherosclerosis of the Guatemalan rural group. This group differed, however, in racial origin: they were known to be predominantly Mayan Indian by their physical appearance, way of life, and the distribution of blood group *O*, which varied from 80 to 96 per cent, depending on the village studied.[3, 4] In contrast, the United States population is known to have a major blood group frequency of approximately 45 per cent type *O*[5], and the upper income Guatemalan population a frequency only slightly higher,[3] which correlates well with the predominantly European origin of this segment of the Guatemalan population. Before accepting environmental variations as responsible for the differences encountered between rural Guatemalans and the other 2 groups it was necessary to be certain that differences in racial origin were not of major significance.

From the Institute of Nutrition of Central America and Panama (INCAP), Guatemala City, Guatemala, and the Department of Nutrition, Harvard School of Public Health, Boston, Mass. The Institute of Nutrition of Central America and Panama is a cooperative activity of Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama, administered by the Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization. INCAP Scientific Publication I-66.

This study was supported in part by grants from the National Heart Institute (grant no. H-2200) of the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.; the Nutrition Foundation, Inc., New York City; the Albert and Mary Lasker Foundation, New York City; the John A. Hartford Memorial Fund; and the Fund for Research and Teaching, Department of Nutrition, Harvard School of Public Health.

In the present study comparable information has been obtained on a group of persons living in rural Costa Rica, under conditions similar to those previously studied in rural Guatemala, except that the Costa Rican population is predominantly European by history, physical appearance, and distribution of the major blood groups.[3]

Material and Methods

The population of the rural area of Turrialba, Costa Rica, was selected because detailed social, economic, agricultural, dietary, and clinical studies had been carried out on this group.[6, 7] This population is European in origin, with essentially no Negro or Indian admixture. In other respects it resembles the rural Guatemalan Indian population previously studied. The results of the clinical and laboratory examinations showed little difference between the rural Costa Ricans and Guatemalans, except for a greater frequency of hookworm anemia among the former. The rural Guatemalans and United States business and professional groups included for comparison in this paper are those previously studied,[1] plus additional determinations in the latter group. Each subject was examined by a physician, and blood pressure, height, and weight were recorded. For the purposes of the present report, subjects with evidences of acute or chronic disease or a blood pressure exceeding 140/90 were excluded from the tabulations.

Dietary Data. Dietary histories were obtained from 140 representative families in the rural area of Turrialba by means of 7-day-diet records. The weekly purchasing pattern of this community facilitated the use of this procedure, which was carried out by a nutritionist familiar with the language, customs, and foods of the people. The nutrient intakes were estimated by means of a food composition table based on the analysis of Central American foods[8] and their dietary allowances modified from those of the National Research Council (U. S.) to conform with local environmental conditions and mean body weights.[9] The collection and calculation of the dietary data on the other 2 groups have been previously described.[1]

Laboratory Data. The blood samples were collected in the field and immediately transported to a central laboratory for centrifugation and recovery of the sera. Serum samples, kept at 0 to 5 C. at all times, were placed in labeled tubes for air shipment to Boston. Lipoproteins were measured with the ultracentrifuge by the method of Gofman and co-workers.[10] Although only the β-lipoprotein S_f 12–20 and S_f 35–100 fractions were measured in the previous study, the values for the S_f 0–12, S_f 12–20, and S_f 20–100 were determined in the Costa Rican sample. Our S_f 20–100 measurements are comparable to the "standard" S_f 20–400 values of Delalla and Gofman.[11] Cholesterol was measured by the method of Abell and associates.[12]

Statistical Data. The laboratory data for each group were tabulated according to sex and decade of age. The tabulations differed from those presented in the previous paper in that no logarithmic transformations of the measurements were made. The degree of skewness of the distribution was sufficiently slight that this transformation was not considered necessary. The relative weights, $\left(100 \times \frac{\text{observed weight}}{\text{desirable weight}}\right)$ were computed for all subjects. For lack of more suitable reference data, the tables of Desirable Weights* of the Metropolitan Life Insurance Company[13, 14] were used for this calculation. The t test was employed to evaluate the significance of difference between means.

Results

A partial summary of the dietary findings in the 3 groups is given in table 1. When compared with the rural Guatemalans previously studied, the diets of the Turrialba rural area population are higher in calories, fat, and cholesterol. The percentage of total calories from fat, although slightly greater than in rural Guatemala, is still less than a third of the percentage given in the United States reports.[15] The amount of protein and fat of animal as compared with vegetable origin, is nearly 3 times greater in the rural Costa Ricans than in the rural Guatemalans, but still much less than for the United States population. It is of interest that the small amount of free fat consumed in Guatemala came from lard, while in Turrialba, some butter and vegetable oil were also used. The cholesterol content of the diets of the 3 groups was estimated and found to be low in the rural Costa Ricans and still lower in the rural Guatemalans.

The levels of cholesterol and lipoproteins of the S_f 12–20 and S_f 20–100 classes for the 3 groups are shown in table 2. The data are grouped according to decade of age and the significance of each comparison is given. When the rural Costa Rican group is compared with the rural Guatemalan group, the serum cholesterol levels tend to be slightly higher, significantly so in 2 age groups for the males and 3 age groups for the females. On the other hand,

* Formerly referred to by the Metropolitan Life Insurance Company as "Ideal Weights."

TABLE 1.—*Approximate Dietary Intake of Study Groups*

	Calories	Cholesterol (mg./day)	Protein (Gm./day)			Fat (Gm./day)			Proportion of calories from fat (%)
			Animal	Veg.	Total	Animal	Veg.	Total	
Rural Costa Rica (Turrialba)	2705	150	17	56	73	25	12	37	12.0
Rural Guatemala (Highlands)	2283	50	6	61	67	9	14	23	7.5
U. S. business and professional workers*	3240	700	65	32	97	104	44	148	41.0

* Derived from available food of 1952.[15]

TABLE 2.—*Serum Lipoprotein and Cholesterol Levels of Rural Costa Ricans, Rural Guatemalans, and North Americans According to Age and Sex*

(Concentrations are mg. per 100 ml. serum; data not adjusted for differences in body weight.)

Age (yr.)	Group	A Rural Costa Rican			B Rural Guatemalan			A compared with B		C United States			A compared with C	
		N	$\bar{X}$	S.D.	N	$\bar{X}$	S.D.		p	N	$\bar{X}$	S.D.		p
Males														
20–29	S_f 12–20	17	21	12	13	24	10	↓		57	31	19	↓	.05
	S_f 20–100		56	44		60	29	↓			66	56	↓	
	Cholesterol		145	31		132	21	↑			213	44	↓	.05
30–39	S_f 12–20	9	28	15	34	31	15	↓		296	37	20	↓	
	S_f 20–100		68	28		67	37	→			81	59	↓	
	Cholesterol		178	38		140	21	↑	0.05		228	48	↓	.05
40–49	S_f 12–20	11	26	11	18	32	17	↓		685	39	21	↓	
	S_f 20–100		65	37		83	49	↓			88	73	↓	
	Cholesterol		170	19		150	48	↑			241	49	↓	.05
50–59	S_f 12–20	13	21	10	16	32	18	↓	0.01	356	39	21	↓	.05
	S_f 20–100		43	24		67	43	↓			82	59	↓	.05
	Cholesterol		162	23		134	32	↑	0.05		244	48	↓	.05
Females														
20–29	S_f 12–20	14	26	14	21	35	20	↓		37	24	14	→	
	S_f 20–100		53	32		79	52	↓			29	19	↑	.05
	Cholesterol		159	30		144	30	↑			196	52	↓	.05
30–39	S_f 12–20	20	27	12	15	41	20	↓	0.01	56	27	17	→	
	S_f 20–100		60	39		89	43	↓	0.01		41	34	↑	
	Cholesterol		179	39		147	24	↑	0.05		209	32	↓	.05
40–49	S_f 12–20	11	25	10	11	45	21	↓	0.05	208	29	15	↓	
	S_f 20–100		52	24		89	45	↓	0.05		39	28	↑	
	Cholesterol		180	32		165	36	↑			225	40	↓	.05
50–59	S_f 12–20	4	35	8	10	43	19	↓		91	39	24	↓	
	S_f 20–100		82	41		65	28	↑	0.01		60	59	↑	
	Cholesterol		191	28		147	33	↑			252	51	↓	.05

the S_f 12–20 fraction tended to be lower in rural Costa Ricans, significantly so in 1 age group for each sex. The S_f 20–100 fraction also tended to be somewhat lower in rural Costa Ricans than in the rural Guatemalans. This difference was significant in females, for the decades 30 to 39 and 40 to 49, with a reversal of this trend in the 50 to 59 age group, probably due to the small number of cases in the latter. The direction of the changes tended to put the rural Costa Ricans closer to the values encountered in the urban United States population, but the magnitude of the differences between the rural Costa Rican and rural Guatemalan populations was small.

When the rural Costa Rican was compared

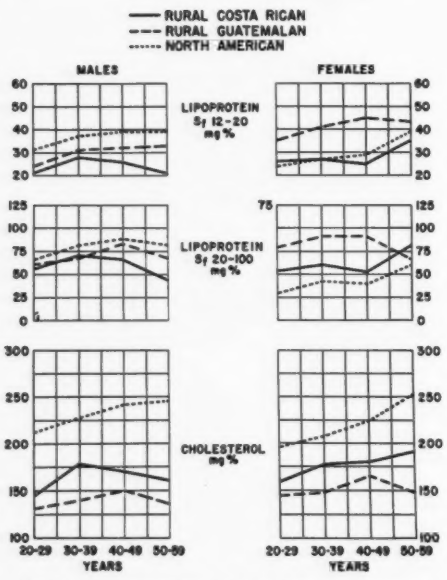


FIG. 1. A comparison of the levels of serum cholesterol and 2 classes of lipoproteins among subjects consuming different diets.

with the urban United States population, the serum cholesterol levels were significantly lower in every decade. However, the trend of the lipoprotein values differed in males and females. Costa Rican males tended to have lower S_f 12–20 and 20–100 values than males of similar age in the United States, although the differences were significant in only about half. On the other hand, a dissociation between cholesterol and lipoprotein was noted in rural Costa Rican women. The S_f 20–100 fraction tended to be significantly higher in the decade 20 to 29. The S_f 12–20 fraction was not significantly different between United States and Costa Rican women.

These trends are shown graphically in figure 1, where the Costa Rican males are intermediate in cholesterol, but tend to be lower in S_f 12–20 and 20–100 levels than the other 2 groups. For the Costa Rican females, the cholesterol and S_f 20–100 levels are seen to be intermediate between the rural Guatemalan and United States groups, but the S_f 12–20 fractions were almost identical in rural Costa Rica and United States.

In the previous study, the levels of the S_f 0–12 lipoprotein fractions were not determined. Table 3 gives the S_f 0–12 concentrations for the rural Costa Ricans and a United States sample done in a different laboratory. The latter is reasonably comparable economically and socially to the United States sample studied in this laboratory. It will be seen that in both sexes and in every decade the S_f 0–12 fractions for the rural Costa Ricans were significantly lower than in the United States population.

TABLE 3.—*Levels of S_f 0–12 Lipoprotein Fractions in Rural Costa Rican and United States Populations*

Age (yr.)	Group A Rural Costa Rican			Group C United States*			A compared with C
	N	$\bar{X}$	S.D.	N	$\bar{X}$	S.D.	p
Males							
20–29	17	197	53	75	302	81	↓ .0
30–39	9	239	48	358	340	88	↓ .0
40–49	11	247	42	313	364	84	↓ .0
50–59	13	220	40	228	367	89	↓ .0
Females							
20–29	14	233	35	86	283	72	↓ .0
30–39	20	268	61	452	304	81	↓ .0
40–49	11	233	41	399	346	81	↓ .0
50–59	4	235	26	269	363	78	↓ .0

* "Standard" S_f 0–12 values[16]; these are slightly lower than "observed" figures as measured on the Costa Ricans.

The rural Costa Ricans showed the same relative weight as the rural Guatemalans for the earlier decades and this remained unchanged through the 50–59 age group, at which time the relative weight of the rural Guatemalan males showed a significant drop. As shown in table 4, the rural Costa Rican females began at a relative weight below that of the rural Guatemalans, and unlike them, did not show any further decrease in relative weight with increasing age. The rural Costa Ricans showed much lower relative weights than the United States subjects. Analysis of covariance had shown in the previous comparison among rural Guatemalans, urban Guatemalans, and a United States urban population sample that relative weight was of

TABLE 4.—*Relative Weights by Age and Sex for Rural Costa Ricans, Rural Guatemalans, and United States Subjects*

Age (yr.)	A Rural Costa Rican		B Rural Guatemalan		A compared with B		C United States		A compared with C	
	$\bar{X}$	$SE_{\bar{X}}$	$\bar{X}$	$SE_{\bar{X}}$		p	$\bar{X}$	$SE_{\bar{X}}$		p
Males										
20–29	94 ± 1.09		96 ± 2.77		↓		107 ± 1.82		↓	.05
30–39	90 ± 2.17		96 ± 1.54		↓	.01	107 ± 0.73		↓	.05
40–49	97 ± 1.62		93 ± 1.89		↑		110 ± 0.45		↓	.05
50–59	94 ± 1.76		76 ± 2.00		↑	.01	111 ± 0.88		↓	.05
Females										
20–29	89 ± 4.00		100 ± 3.41		↓	.01	103 ± 2.47		↓	.05
30–39	91 ± 3.02		93 ± 2.58		↓		107 ± 2.55		↓	.05
40–49	95 ± 5.05		94 ± 3.92		↑	.01	106 ± 1.55		↓	.05
50–59	90 ± 4.26		83 ± 3.33		↑		106 ± 2.53		↓	.05

minor importance in influencing serum lipid levels. This analysis was repeated for the comparison between the rural Costa Rican and United States group, with the same results.

DISCUSSION

These observations indicate that the differences previously encountered between the rural Guatemalan population and the urban groups in Guatemala and the United States were not due to racial factors. Furthermore, the differences in serum lipids between the rural Costa Ricans and rural Guatemalans are in general small and not statistically significant. It is of interest that these differences are almost always in the direction of the urban business and professional population in the United States and Guatemala, so that the Costa Ricans can be said to have gone a very small part of the distance toward the type of serum cholesterol and lipoprotein relationships found in the United States.

Table 1 shows that urban Costa Ricans do have slightly more animal protein, slightly more fat, a higher percentage of calories from fat, and more cholesterol in their diets than do the rural Guatemalans. The evidence that dietary cholesterol has no relation to serum cholesterol levels within the range of cholesterol intake under consideration is convincing.[17, 18] If the difference in serum cholesterol can be attributed to the difference in fat intake, as has been suggested by Keys,[19, 20] it may be somewhat discouraging from the point of view of prevention to note that differences as small as those existing between these 2 rural populations may have a detectable effect on cholesterol levels. However, assuming serum cholesterol levels correlate with the occurrence of atherosclerosis, the upper limits beyond which the development of atheromata are accelerated are still unknown.

Attention has also been called to the similarity between the predominantly vegetable diet consumed by persons in rural Central America and the "rice diet" regimen for the treatment of essential hypertension. In the latter, Hatch's group[17] has reported a lowering of cholesterol values in most cases together with a 9 per cent increase in S_f 12–20 and a 99 per cent rise in S_f 20–100 values. This was associated with an increase in serum neutral fat.

The suggestion has been made that some factor in vegetable protein diets, apart from the major nutrients, might be responsible for a decrease in serum cholesterol levels in persons consuming low-fat diets. Sitosterol has been studied as an example of such a substance.[21] However, it has been difficult to conceive of a factor that would be common to low-fat diets in all of the various parts of the world in which low serum cholesterol levels have been encountered. Malmros and Wigand[22]

have reported that a fall in serum cholesterol levels accompanied the institution of a diet rich in corn oil in 8 cases of familial hypercholesterolemia. They suggested that these effects might be due to the high essential fatty acid content of corn oil, which contains 57 per cent linoleic acid. This suggestion is supported by the recent observations of Lever and Waddell,[23] Kinsell and co-workers,[24] Bronte-Stewart,[25] and Ahrens.[26] However, most of these studies have been on few patients and for short periods of observation. When 1000 calories of an unsaturated vegetable oil (peanut) with 22 per cent linoleic acid were incorporated into the daily diets of 25 men for a period of 4 weeks, we observed a marked drop in cholesterol after 1 or 2 weeks, but by the fourth week the cholesterol values were mostly back at starting levels.[27] Thus, the decrease in serum cholesterol reported to follow the generous administration of some oil rich in essential fatty acids may turn out to be only transient when added to the daily diet. Nevertheless, it is of interest that the high-corn diets of Central America, although low in total fat, do at least provide a generous proportion of the essential fatty acid, linoleic acid.

The results again indicate that under the conditions prevailing in Central America, particularly in females, a definite dissociation between the levels of serum lipoprotein and cholesterol occurs. The Guatemalan females can no longer be said to be unique in combining low cholesterol levels with high lipoprotein levels when compared with age-matched North American females, for the Costa Rican females also show this phenomenon in the S_f 20–100 lipoprotein fractions. This discrepancy raises the question as to which fractions in the lipoprotein complex system are involved in the lower levels of cholesterol in the blood stream under the environmental influences prevailing in rural Guatemala and Costa Rica. The cholesterol associated with the various lipoprotein fractions accounts for at least 95 per cent of the total.[28] The cholesterol content of the S_f 0–12 fraction alone has been given as approximately 33 per cent.[27-30] From the results of the present study it appears that most of the difference in cholesterol levels can be accounted for by the low levels of the S_f 0–12 fraction.

The question may be raised as to whether the rural Costa Rican population is as free from the complications of atherosclerosis as the rural Guatemalan population. Preliminary information being collected by one of us (C. T.) in cooperation with Dr. Rodolfo Céspedes in Costa Rica indicates that the Costa Rican rural population does, in fact, share in this relative immunity from coronary heart disease and other complications of atherosclerosis. If this is true, our data on both the Guatemalans and Costa Ricans, indicating rather minor differences in the serum concentrations of the lipoproteins, S_f 12–100, between these groups and the United States population, but large and significant differences in the S_f 0–12 and cholesterol concentrations between the Costa Rican and United States groups, suggest that these latter 2 fractions may be more intimately related to the development of atherosclerosis than the S_f 12–100 fractions.

There is no doubt that the rural and poor urban populations of Central America consume much less fat than most persons in the United States, derive a far smaller percentage of their total calories from this class of nutrient, and utilize different kinds of fats. Other known differences in the dietary data include the amount of animal protein, the number of calories from refined carbohydrates, and the percentage of crude fiber. In addition, vitamin A and riboflavin intakes are lower and the mineral composition of the diets differ. It is also conceivable that there are other specific factors in the Central American diets that can serve to depress the serum cholesterol. Furthermore, the relative body weights of the rural population are less and they are more active physically. For these reasons, it would be premature to assert which specific environmental factors are the ones responsible for the lower serum cholesterol and freedom from the complications of atherosclerosis of the lower income groups of Central America. Fortunately, the Central American area offers a very favorable opportunity for the continuing investigation of this problem.

Summary

The total cholesterol and major beta-lipoprotein fractions were determined in a group of 99 men and women living in the rural zone of Turrialba, Costa Rica, and subsisting on diets low in fat and animal protein. These measurements were compared with North Americans and rural Guatemalans previously investigated.

At all ages studied the Costa Rican subjects, both male and female, were shown to have mean cholesterol values that were slightly higher than the rural Guatemalans, but much lower than the North Americans. There was little evidence among the Costa Ricans of the tendency for serum cholesterol to increase with age. The S_f 12–20 and 20–100 levels in the rural Costa Rican males were only slightly lower and in the females were frequently higher than in the North Americans. They tended to be lower, however, than in the rural Guatemalans previously studied. The S_f 0–12 levels were lower in the rural Costa Ricans than in the North Americans and this difference was sufficient to account for most of the differences in cholesterol levels.

The greater leanness of the rural Costa Rican was shown not to be a significant factor in the lower cholesterol values. Since the rural Costa Rican population was of European origin in contrast to the predominantly Mayan Indian of the rural Guatemalan group previously studied, the similarity of the results in both populations would seem to eliminate racial factors from serious consideration and to confirm the hypothesis that environmental factors, most likely nutritional, are responsible for the differences observed between rural Central Americans and North Americans.

In view of the supposed freedom of Central American rural and low income urban populations from the complications of atherosclerosis it is important that the dietary and other environmental factors be identified that may be responsible for these differences.

Since there are only minor differences in the concentration of the S_f 12–100 lipoproteins in the United States and Central American groups, but large differences in the serum cholesterol and S_f 0–12 lipoproteins, the latter 2 fractions may be more closely related to the development of atherosclerosis than the lipoproteins with high flotation rates.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. Eleanor Y. Lawry and Miss Mary McCann in carrying out the lipoprotein measurements and assistance in the preparation of the manuscript. Dr. Carlos Díaz Amador, Chief of the Nutrition Section of the Public Health Department of Costa Rica, assisted in the collection of blood samples and clinical data. Dietary data on the Costa Rican population were furnished by Margaret Fiester.

Summario in Interlingua

Le cholesterol total e le major fractiones de lipoproteina beta esseva determinate in un gruppo de 99 homines e feminas habitante le zona rural de Turrialba in Costa Rica e vivente con dietas a basse contento de grassia e proteina animal. Iste mesurationes esseva comparate con datos obtenite in previe investigationes de nord-americanos e guatemalanos.

Esseva constatate que le costaricanos de ambe sexos e de omne etates representate in le studio habeva valores medie de cholesterol que esseva levemente plus alte que illos del guatemalanos rural sed multo plus basse que illos del nord-americanos. In le costaricanos le tendentia de cholesterol seral de augmentar se con le etate del subjectos esseva pauco evidente. Le nivellos S_f 12–20 e 20–100 in masculos rural de Costa Rica esseva solmente pauco plus basse que in nord-americanos; in femininas illos esseva frequentemente plus alte. Tamen, iste valores tendeva a esser plus basse que in le previemente studiate guatemalanos rural. Le nivellos S_f 0–12 esseva plus basse in le costaricanos rural que in le nord-americanos, e iste differentia sufficeva a coperir le plus grande parte del differentias in le nivellos de cholesterol.

Esseva monstrate que le plus grande magressa del costaricano rural non esseva un factor significative in le causation del plus basse valores de cholesterol. Proque le subjectos rural in Costa Rica esseva de origine europee durante que le previemente studiate gruppo de guatemalanos rural esseva predominantemente indianos mayan, le similaritate del resultatos obtenite in le duo populationes pare

eliminar le possibilitate que factores racial debe esser prendite in consideration e confirma le hypothese que factores ambiental, probabilissimemente nutritional, es responsabile pro le differentias observate inter centro- e nord-americanos rural.

Viste le observation que le populationes rural a basse revenitos in America Central es libere del complicationes de atherosclerosis, il es importante identificar le factores dietari e alteremente ambiental que es responsabile pro iste differentias.

Proque il existe solmente minor differentias in le concentrationes del lipoproteinas a S_f 12–100 inter le gruppos statounitese e centro-american sed grande differentias in le cholesterol seral e le lipoproteinas a S_f 0–12, iste ultime fractiones es forsan plus directemente connectite con le disveloppamento de atherosclerosis que le lipoproteinas a S_f 12–100.

REFERENCES

[1] Mann, G. V., Muñoz, J. A., and Scrimshaw, N. S.: The serum lipoprotein and cholesterol concentrations of Central and North Americans with different dietary habits. Am. J. Med. **19:** 25, 1955.

[2] Tejada, C. E., and Gore, I.: Unpublished data, 1956. Comparison of atherosclerosis in Guatemala and New Orleans. Submitted for publication.

[3] Instituto de Nutricion de Centro America y Panama. Unpublished data, 1956.

[4] Aguirre, F., Tandon, O. B., and Scrimshaw, N. S. Distribution of blood groups in Guatemalan Indians. Rec. Genet. Soc. Am. **22:** 63, 1953.

[5] Boyd, W. C.: Genetics and the Races of Man. Boston, Little, Brown and Company, 1950.

[6] Scrimshaw, N. S., Morales, J. O., Salazar B. A., and Loomis, C. P.: Health aspects of the community development project, rural area, Turrialba, Costa Rica. Am. J. Trop. Med. & Hyg. **2:** 583, 1953.

[7] Loomis, C. P., Morales, J. O., Clifford, R. A., and Leonard, O. E.: Turrialba. Social Systems and the Introduction of Change. Glencoe, Ill., The Free Press, 1953.

[8] Instituto de Nutricion de Centro America y Panama: Tercera edición de la tabla de composición de alimentos de Centro América y Panamá. Bol. Ofic. san. panam., Suppl. **1:** 129, 1953.

[9] —: Recomendaciones nutricionales para las poblaciones de Centro América y Panamá. Bol. Ofic. san panam., Suppl., **1:** 119, 1953.

[10] Gofman, J. W., Lindgren, F., Elliott, H. A., Mantz, W., Hewitt, J., Strisower, B., and Herring, V.: The role of lipids and lipoproteins in atherosclerosis. Science **11:** 166, 1950.

[11] Delalla, O. F., and Gofman, J. W.: Ultracentrifugal analysis of serum lipoproteins. In Methods of Biochemical Analysis vol. I. Edited by Glick, D. New York, Interscience Publishers, Inc., 1954, p. 459–478.

[12] Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A simplified method for estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. & Chem. **195:** 357, 1952.

[13] Ideal Weights for Women. Statistical Bulletin. Metropolitan Life Insurance Company, **23:** 6, 1942.

[14] Ideal Weights for Men. Statistical Bulletin. Metropolitan Life Insurance Company, **24:** 6, 1943.

[15] United States Department of Agriculture: Consumption of food in the United States, 1909–1952. U.S.D.A. Misc. Public. No. 62, 1953.

[16] Glazier, F. W., Tamplin, A. R., Strisower, B., Delalla, O. F., Gofman, J. W., Dawber, T. R., and Phillips, E.: Human serum lipoprotein concentrations. J. Gerontol. **9:** 395, 1954.

[17] Hatch, F. T., Abell, L. L., and Kendall, F. E.: Effects of restriction of dietary fat and cholesterol upon serum lipids and lipoproteins in patients with hypertension. Am. J. Med. **19:** 48, 1955.

[18] Keys, A., Anderson, J. T., Mickelsen, O., Adelson, S. F., and Fidanza, F.: Diet and serum cholesterol in man: Lack of effect of dietary cholesterol. J. Nutrition **59:** 39, 1956.

[19] —: Mode of life and the prevalence of coronary heart disease. Arteriosclerosis. A Symposium presented by the Minnesota Heart Association and the University of Minnesota. September 7–9, 1955. University of Minnesota, 1956, p. 28.

[20] —: Human atherosclerosis and diet. Circulation **5:** 115, 1952.

[21] Best, M. M., Duncan, C. H., Van Loon, E. J., and Wathen, J. D.: The effects of sitosterol on serum lipids. Am. J. Med. **19:** 61, 1956.

[22] Malmros, H., and Wigand, G.: Treatment of hypercholesteremia. Arteriosclerosis. A Symposium presented by the Minnesota Heart Association and the University of Minnesota. September 7–9, 1955. University of Minnesota, 1956, p. 114.

[23] Lever, W. F., and Waddell, W. R.: Idiopathic hyperlipemia and primary hypocholesteremic xanthomatosis. VII. Effect of intravenously administered fat on the serum lipids. J. Invest Dermat. **25:** 233, 1955.

[24] K NSELL, L. W., FRISKEY, R. W., MICHAELS, G. D., AND BROWN, F. R.: Effect of a synthetic triglyceride on lipid metabolism. J. Clin. Nutrition **4:** 285, 1956.

[25] I ONTE-STEWART, B., ANTONIS, A., EALES, L., AND BROCK, J. F.: Effects of feeding different fats on serum-cholesterol level. Lancet **1:** 521, 1956.

[26] A HRENS, E. H., JR., TSALTAS, T. T., HIRSCH, J., AND INSULL, W., JR.: Effects of dietary fats on the serum lipids of human subjects. J. Clin. Invest. **34:** 918, 1955.

[27] I EPARTMENT OF NUTRITION: Harvard School of Public Health. Unpublished data, 1956.

[25] LINDGREN, F. T., ELLIOTT, H. A., AND GOFMAN, J. W.: The ultracentrifugal characterization and isolation of human blood lipids and lipoproteins with applications to the study of atherosclerosis. J. Phys. Colloid Chem. **55:** 80, 1951.

[29] HAVEL, R. J., EDER, H. A., AND BRAGDON, J. H.: The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum, J. Clin. Invest. **34:** 1345, 1955.

[30] HILLYARD, L. A., ENTENMAN, C., FEINBERG, H., AND CHAIKOFF, I. L.: Lipid and protein composition of four fractions accounting for total serum lipoproteins. J. Biol. Chem. **214:** 79, 1955.

RUPTURE OF THE HEART

I will add another observation: A noble Knight Baronet, Sir Robert Darcie, father to the Son-in-Law of the most learned man, and my very great friend and a famous Physician, Dr. Argent, about the middle of his age, did often complain of an oppressive pain in his breast, especially in the night time, so that sometimes being afraid of collapsion of spirits, sometimes fearing suffocation by a Paroxisme, he led an unquiet and anxious life, using the Counsell of all Physicians, and taking many things in vain; at last the disease prevailing, he becomes cachectick, and Hydropick, and at last opprest in a signal Paroxism, he dyed. In his Corps, in the presence of Dr. Argent, who at that time was President of the College of Physicians, and Dr. Gorge, a rare Divine, and a good Preacher, who was at that time Minister of that Parish, by the hinderance of the passage of the blood out of the left ventricle into the arteries, the wall of the left ventricle it self (which is seen to be thick and strong enough) was broken, and poured forth blood at a wide hole, for it was a hole so big, that it would easily receive one of my fingers.—WILLIAM HARVEY, *De Circulatione Sanguinis*, 1649.

Valvular Pulmonary Stenosis with Intact Ventricular Septum

Clinical and Physiologic Response to Open Valvuloplasty

By S. Gilbert Blount, Jr., M.D., Jack van Elk, M.D., Oscar J. Balchum, M.D., Ph.D., and Henry Swan, M.D.

Clinical and physiologic studies have been carried out in 25 patients following surgical correction of congenital valvular pulmonary stenosis. The patients were operated upon under conditions of hypothermia and circulatory occlusion and the approach to the valve was transarterial, permitting plastic repair of the stenotic pulmonary valve with unimpaired vision and a dry operative field. The systolic pressure gradient between the right ventricle and the pulmonary artery has been completely abolished in 17 of the 25 patients. The results as reported in this series are considered to be superior to those obtained with the blind transventricular approach and the operative mortality certainly compares favorably with the transventricular approach.

VALVULAR pulmonary stenosis with an intact ventricular septum is a common congenital anomaly. Frequently this defect is not detected early in life as the completely asymptomatic course does not bring the child to the attention of a physician. The increase in periodic physical examinations of school children in recent years has led to the discovery of a greater number of individuals with this type of congenital heart disease. However, the clinical findings are easily misinterpreted, and because of the complete lack of symptoms and the normal heart size the severity of this anomaly has frequently not been appreciated. The true significance of this entity and its potential danger, however, is now more generally realized.

Several forms of corrective surgery for valvular pulmonary stenosis have been developed. The transventricular approach of Brock has been widely employed; however, evaluation of the operative results both at this institution and elsewhere has led to the conclusion that this approach often does not satisfactorily relieve the stenosis.[1–5]

From the Departments of Medicine and Surgery, University of Colorado School of Medicine, Denver, Colo.

This study was supported in part by a grant from the American Heart Association and in part by a U. S. Public Health Service Grant H-1208.

Dr. van Elk is a Research Fellow of the Colorado Heart Association, Dr. Balchum is a Research Fellow of the American Heart Association.

The application of hypothermia with circulatory occlusion has permitted open heart surgery, whereby the type and the degree of the stenosis can be evaluated and valvuloplasty performed with deliberation. Our experience with this approach in 38 patients has demonstrated that the mortality is no greater than with the blind ventricular approach and that results are superior.

Materials and Methods

A total of 38 patients has been operated on by this technic. Ten patients were cyanotic. The 2 deaths in the series were in this group.

This study concerns itself mainly with the first 25 consecutive patients who have been evaluated before and after surgery from a clinical and physiologic standpoint. The remaining 13 patients have been operated upon too recently for follow-up studies. These 25 patients can be divided into 2 groups, 15 patients with an intact atrial septum and 10 patients with associated functional or anatomic atrial septal defect (tables 1 and 2).

All patients were operated via a transarterial approach under hypothermia and circulatory occlusion.[6] The stenotic valve was incised and partially excised in the first 3 patients. In all other patients the stenotic valve was incised along the commissures, without removal of valve tissue. The first 3 patients have now been followed for 3 to 3½ years, while all other patients have been followed for a period of from a few months to 3 years.

All patients except 1 were catheterized prior to operation, and all were recatheterized following surgery. Strain gages and a Hathaway oscillograph were used for the recording of pressures.

TABLE 1.—*Pressures in Fifteen Patients with Valvular Pulmonary Stenosis and Intact Atrial Septum*

Patient Number	Sex	Age	Preoperatively				Postoperatively			
			PA	Grad.	RV	Sat.	PA	Grad.	RV	Sat.
1	F	9	17/7	125	142/−2	94.7	15/3	4	19/−5	95.6
2	F	8	18/12	92	110/3	93.2	32/9	0	32/−1	92.7
3	F	8	18/9	101	119/−5	96.6	25/9	4	29/6	94.8
4	M	32	25/7	125	150/5	95.2	20/12	22	42/5	95.0
5	M	5	17/13	48	65/3	98.5	21/10	14	35/1	93.5
6	F	4½	19/12	77	96/9	95.8	27/18	8	35/4	98.6
			32/16*	68	100/12		56/30*	12	68/10	
7	F	3	30/16	105	135/11	99.8	33/12	17	50/−2	97
8	F	3	31/17	126	157/5	95.7	49/22	25	74/12	92.8
							43/20†	24	67/16	
9	M	3	25/13	96	121/6	92	18/8	9	27/2	94.7
10	F	33	23/15	167	190/27	93.2	27/13	59	86/10	93.6
11	F	17	24/8	63	87/12	92.8	37/12	11	46/12	92.9
12	M	3	15/10	155	170/12	91.6	38/23	12	50/15	90.4
13	M	6	30/20	175	205/9	99.8	26/16	33	59/13	92.6
14	F	1	15/11	127	142/0	91.4	26/13	7	33/0	96.7
15	F	10	18/12	158	176/9	97.5	20/10	25	45/9	95.5

PA = Pressures in mm. Hg in pulmonary artery (PA), right ventricle (RV) and systolic pressure gradient (Grad.) between them.

Sat. = Peripheral arterial blood oxygen saturation in percentages.

* Second reading following exercise.

† Second postoperative catheterization 1 year following surgery.

TABLE 2.—*Pressures in Ten Patients with Valvular Pulmonary Stenosis and Atrial Defect*

Patient Number	Sex	Age	Preoperatively				Postoperatively			
			PA	Grad.	RV	Sat.	PA	Grad.	RV	Sat.
16	F	2	—	—	115/4	80.0	15/9	14	29/7	86.2
17	M	9	17/7	125	142/−2	86.0	15/3	4	19/−5	95.5
18	M	1	—	—	—	—	17/9	41	58/−1	90.6
							30/16*	23	53/3	88.5
19	M	2½	18/10	75	93/8	84.0	46/25	19	65/5	79.0
							27/14*	20	47/4	
20	M	1	—	—	180/10	—	25/10	15	40/3	—
21	F	13	—	—	120/5	78	27/12	33	60/3	73.6
							23/13	22	45/8	91
22	F	1½	17/8	173	190/12	—	29/11	5	34/8	—
23	M	4	28/23	145	173/11	81.2	39/23	26	65/5	85.2
24	F	6	32/20	38	70/4	94.0	26/10	0	26/−2	93.8
25	M	11	23/13	114	137/11	86	43/13	2	45/3	85

PA = Pressures in mm. Hg in pulmonary artery (PA), right ventricle (RV) and systolic pressure gradient (Grad.) between them.

Sat. = Peripheral arterial blood oxygen saturation in percentages.

* Second postoperative catheterization 1 year following surgery.

RESULTS

Clinical Observations

The majority of the patients were young children, only 3 were older than 15 years.

Of the 15 patients with an intact atrial septum (table 1), 7 patients were asymptomatic while the other 8 revealed a slight degree of dyspnea and fatigue, only with sustained exertion. The dyspnea was never severe, and the fatigue was the more prominent complaint,

although this was usually difficult to evaluate, particularly in children. No cyanosis was noted in this group. Following operation all 8 patients reported an improvement in exercise tolerance, and all but 1 were considered to be normal in this respect.

Eight of the 10 patients with a defect in the atrial septum (table 2) were cyanotic. Patient no. 24 was acyanotic and on fluoroscopy showed an increased vascularity of the lung fields; at cardiac catheterization a left-to-right shunt was found at the atrial level. Patient no. 25 was not cyanotic; however bidirectional shunting of blood at the atrial level was demonstrated at cardiac catheterization. After surgery 2 patients became acyanotic, the cyanosis decreased significantly in 2, while in the remaining 4 patients no definite change in color was observed. All patients in this group were limited in their exercise tolerance: 6 had slight limitation; 2 patients, (no. 21 and 25) could not walk more than a few blocks and became more deeply cyanotic on exertion; patient no. 20 had spells of severe cyanosis and dyspnea; and patient no. 18, a deeply cyanotic infant, was in congestive failure during the month prior to surgery. Without exception all patients in this group showed marked improvement in their exercise tolerance following surgery.

A palpable thrill was observed in all patients of both groups. Postoperatively the thrill disappeared in all but 3 patients. A harsh, systolic murmur was audible in all patients. It was of grade IV to VI in intensity in 21 and maximum in the first left intercostal space at the sternal border; 4 patients had only a grade II to III murmur. Following operation the murmur decreased in intensity to grade II or III in all but 4 patients, in whom it was grade IV. The murmur never disappeared completely.

A diastolic murmur of pulmonary insufficiency was noted following operation in the 3 patients in whom the pulmonary valve was partially excised and in 8 of the remaining 22 patients.

Electrocardiography

A tall R wave with a ventricular activation time exceeding 0.03 second was present in lead V_3R and V_1 in all patients in this study. A deep S wave, usually greater than 3 mm. and as great as 14 mm. was present in V_6 and ranged from 3 to 12 mm. in V_7. A significant decrease in the height of the R wave in leads V_3R and V_1 and in the depth of the S wave in leads V_6 and V_7 was observed in all patients followed for a period of more than 6 months after operation (figs. 1 and 2). The late R deflection in lead aV_R also diminished. A striking change

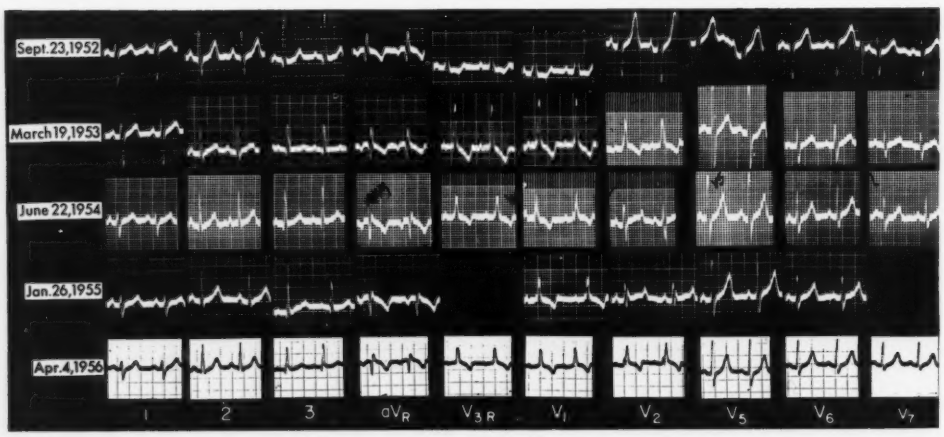


FIG. 1. Electrocardiographic changes in patient J. K. (10 years old) in whom the valve commissures were excised and some valve substance was removed. Note the continuing decrease of the height of the R wave in V_{3R}, V_1, and V_2, the decrease of the depth of the S wave in V_6 and V_7, and the decrease in the late R deflection of aV_R. (Operation; March 10, 1953.)

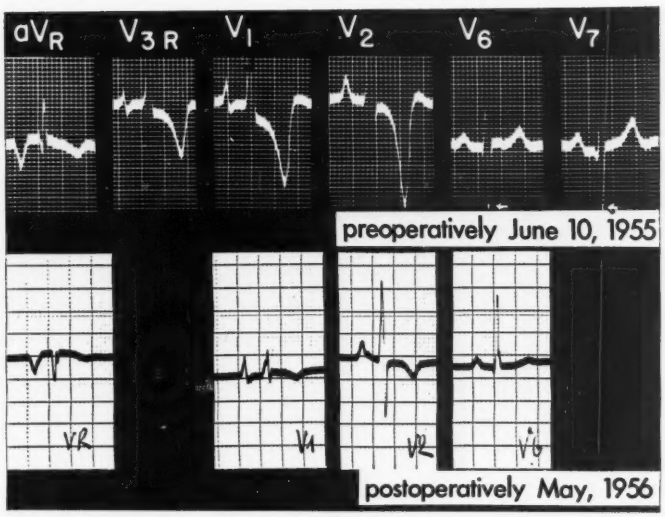


FIG. 2. Electrocardiographic changes in a patient L. E. (15 years old) with valvular pulmonary stenosis and a patent foramen ovale. (Operation; June 16, 1955.)

was also noted in 5 patients, with a change from a tall upright deflection in V_1 to an rSR′ pattern.

Radiography

Decreased vascularity of the peripheral lung fields was observed prior to surgery in all the cyanotic patients. In 1 acyanotic patient (no. 24), the vascularity was increased, and it was considered normal in the remaining patients. No significant change in the peripheral vascularity has been definitely detected following operation.

The main pulmonary artery was enlarged in all patients and has not changed so far following surgery. The right and left pulmonary arteries were of normal or slightly increased size. The left pulmonary artery was often bigger than the right pulmonary artery.

The main pulmonary artery showed increased activity and pulsations in all patients. This hyperactivity contrasted with the relatively quiet right and left pulmonary arteries. There was an increase in activity of the latter vessels following surgery in 17 patients; in 2 patients the right pulmonary artery did not show pulsations postoperatively and in the remainder it was difficult to estimate whether or not activity of the right and left pulmonary arteries had increased.

All patients demonstrated an enlarged right atrium and a cardiac configuration suggesting right ventricular hypertrophy. This pattern remained unchanged following surgery. A slight increase in over-all heart size was detected following the surgical correction of the pulmonary stenosis in 10 patients. This increase in heart size was slight and occurred immediately following operation; no further enlargement has been observed, and the over-all size of the heart, to date, is considered to be within normal limits.

Pathology

The valvular deformities seem to fall into 2 categories, one perhaps representing a more advanced form of a single developmental process. In type I, more commonly seen in the younger patients and particularly associated with the higher ventricular pressures and larger gradients, the valve is composed of an elongated cone, more or less symmetrical, tapering to a small circular orifice, usually 1 to 3 mm. in diameter. The valve structure is not much thickened or fibrosed. Evenly spaced around the sulcus of the valve ring are 3 tiny elevations of fibrous tissue representing a rudimentary attempt at commissure formation.

More commonly seen in adult patients is what we have termed the type II deformity.

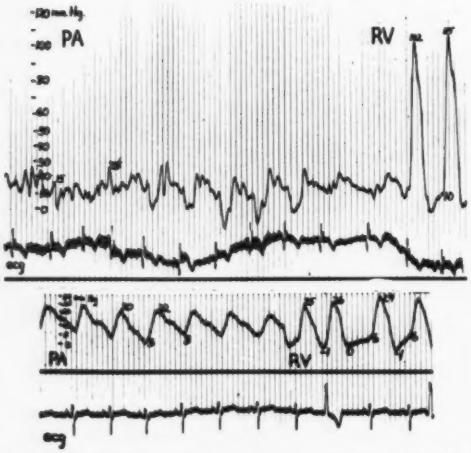


FIG. 3. Right pulmonary artery (*PA*) and right ventricular pressure (*RV*) before (*top*) and after (*bottom*) operation in patient 9.

The valve is much shorter, and consists of 3 well-defined cusps, with fused commissures extending the entire distance to the orifice, which is irregular in shape, with diameters of 2 to 6 mm. The defect is asymmetrical so that the jet stream may be ejected obliquely into the enlarged artery beyond. The rim of the defect is irregularly thickened and very firm and rubbery in consistency, offering considerable resistance to the cutting instrument. The commissures are also thickened, and offer the opportunity to the surgeon to create intact semilunar valves by very precise incisions through the center of the commissures.

Hemodynamics

The right heart and pulmonary artery pressures are recorded in tables 1 and 2. The postoperative data were obtained within a 3-month period following surgery in all patients. Data obtained at second postoperative catheterization 1 year following surgery in 4 patients are also included.

The preoperative right ventricular systolic pressures were found to range from 100 to 142 mm. Hg in the 3 patients (no. 1, 2, and 16) in whom the valve was partially excised, but became normal in all 3 patients following operation. The systolic pressure gradient between the right ventricle and the pulmonary artery

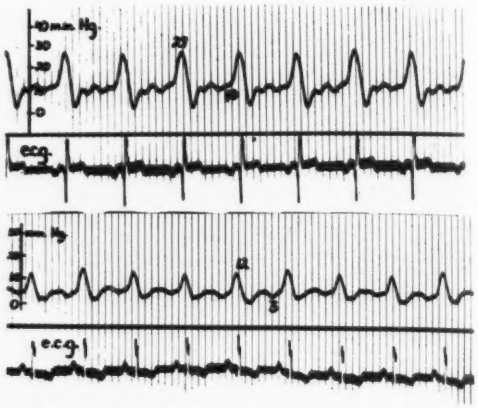


FIG. 4. Right atrial pressure before (*top*) and after (*bottom*) operation in patient 10.

disappeared or was reduced to the minimal value of 14 mm. The pulmonary artery diastolic pressure decreased to lower than normal levels in 1 patient.

Partial excision of valve tissue has been abandoned as unnecessary; therefore our main concern at the present time is with the hemodynamic data obtained before and after operation in the 22 remaining patients.

In them the systolic pressure gradient between the right ventricle and the pulmonary artery, which ranged from 38 to 175 mm. Hg preoperatively, was reduced to less than 20 mm. Hg in 14 patients (fig. 3). Particular attention is to be given to the remaining 8 patients who had a postoperative gradient of over 20 mm. Hg. An additional interesting finding is that the systolic pressure in the pulmonary artery in 6 patients increased to higher than normal levels postoperatively, ranging from 37 to 49 mm. Hg. In a seventh patient (no. 6) the systolic pulmonary artery pressure was normal at rest (27 mm. Hg) but increased during exercise to 56 mm. Hg (table 1).

The right atrial pressure was reduced following surgery (fig. 4) in patients in whom this pressure was high preoperatively, and in whom the pressure record showed a giant a-wave.

In the patients with a defect in the atrial septum, 9 revealed cyanosis or peripheral arterial oxygen unsaturation as evidence of a

right-to-left shunt through the defect. Following operation 2 patients (no. 17 and 21) showed an increase in their peripheral arterial oxygen saturation to normal or nearly normal levels.

No peripheral arterial blood was obtained prior to surgery in patient no. 18, who was severely cyanotic and in congestive failure. Postoperatively the oxygen saturation was 87.7 per cent, probably a very significant increase.

In 2 other patients the oxygen content of the peripheral arterial blood was not determined before and after operation. In the remaining 4 patients the peripheral arterial oxygen saturation has not changed significantly following surgery for periods of a few months to 2 years.

Patient no. 24 demonstrated a decrease in the right ventricular systolic pressure from 70 to 40 mm. Hg postoperatively, but the left-to-right shunt increased. Following closure of the atrial septal defect at a later date the right ventricular pressure was reduced to normal with complete obliteration of the systolic pressure gradient between the right ventricle and pulmonary artery (table 2).

Patient no. 25 also demonstrated an increase in the volume of the left-to-right shunt through the defect in the atrial septum following valvuloplasty.

Discussion

Mortality

The 4 largest groups of patients with valvular pulmonary stenosis and intact ventricular septum that have been operated upon by the transventricular approach are those of Campbell and Brock,[2] Hosier,[3] Lillehei,[4] and Silverman.[5] Campbell and Brock have reported a total of 58 patients with 8 deaths (14 per cent). There was a significant difference in the mortality with the presence or absence of cyanosis. In 33 acyanotic patients with valvular pulmonary stenosis there was but 1 death, while in 25 cyanotic patients there were 7 deaths. Hosier and associates have reported on a series of 86 patients of whom 7 died (8 per cent). Three patients died (14 per cent) of 21 reported by Silverman and associates; these 3 were in congestive failure with marked cardiomegaly. The transventricular approach for the relief of pulmonary valvular stenosis has been performed in only 6 patients in our institution with 1 death. Thus, the over-all mortality from the transventricular approach may be considered to be about 10 per cent.

Although the present series is relatively small, it is the largest one that has been reported in which the direct approach has been applied. Thirty-eight patients have been operated upon with 2 deaths, a mortality of 5 per cent. Both patients who died were cyanotic; there have been no deaths in 30 acyanotic patients.

The first patient who died was a 7-month-old infant with a large heart, marked cyanosis, and congestive failure. The peripheral arterial oxygen saturation was 47 per cent and the pressure in the right ventricle was 108/35 mm. Hg. Operation was considered an emergency measure. A severe valvular pulmonary stenosis was found, the orifice being 1.5 mm. in diameter. Operation was without event, the patient returned to her room in good condition. She died suddenly and unexpectedly 12 hours postoperatively. Unfortunately, a postmortem examination was not permitted. The other patient who died was a 10-year-old boy. He was cyanotic and had a peripheral arterial oxygen saturation of 75 per cent and a hematocrit value of 85 per cent. The right ventricular pressure was 175/9 mm. Hg. Severe valvular pulmonary stenosis was found at operation and was relieved with difficulty. Preoperative cardiac catheterization had revealed a defect in the atrial septum and this finding was confirmed by palpation at operation. After relief of the pulmonary stenosis it was decided to repair the atrial septal defect, but before this was completed the patient developed ventricular fibrillation. The heart beat was restored to a regular rhythm but the patient died 5 hours later of a bleeding diathesis.

Although this series is relatively small, it is considered that the operative risk of 5 per cent with the direct approach under hypothermia is certainly not greater and in fact may be less than that of transventricular approach.

Pulmonary Insufficiency

The creation of insufficiency resulting from the excision of valve substance has been criticized.[2] The 3 patients in whom the valve was partially excised in addition to the incision along the commissures, have now been followed for 3½ years. All have definite auscultatory evidence of pulmonary insufficiency. The degree of pulmonary insufficiency is not considered significant, however, as the diastolic pressure in the pulmonary artery is within normal limits in 2 of these patients and is slightly decreased in the remaining 1. Careful evaluation at this time reveals that all 3 are active, leading entirely normal lives with no symptoms whatsoever. There has been no increase in the size of the heart, which is now within normal limits. The electrocardiogram has revealed regression of the evidence of right ventricular hypertrophy in all 3 patients (fig. 1). These findings suggest that the degree of pulmonary insufficiency in these patients is not of hemodynamic significance.

Experimental excision of pulmonary valve cusps in the dog does not result in any noticeable detrimental effects upon the heart[7–11]; only if all 3 cusps are completely excised does the right ventricle dilate and the right heart fail.[11] The low diastolic pressure gradient normally existing between the pulmonary artery and the right ventricle, which is due to the low pulmonary vascular resistance, apparently results in an insignificant reflux of blood into the right ventricle, when the insufficiency of the pulmonary valve is mild.

However, it is again emphasized that only a minimal amount of actual valve substance was removed in the first 3 patients, and that no valve tissue has been excised in the last 35 patients. In 8 of the latter patients a murmur of pulmonary insufficiency was also audible. The degree of pulmonary insufficiency in these patients is not considered to be of hemodynamic significance, since the diastolic pressure in the pulmonary artery was over 8 mm. Hg in all. The development of a postoperative pulmonary diastolic murmur has also been reported by authors employing the transventricular technic.[2]

Thus, even when no valve tissue is excised, a slight degree of pulmonary insufficiency may occasionally result in some patients, but even when it occurs, it is not considered to be of hemodynamic nor of clinical significance.

Clinical Observations

Seven patients were asymptomatic prior to surgery. Fourteen patients had symptoms of minimal dyspnea and fatigue on exertion. Two patients (no. 21 and 25) were moderately incapacitated, while the remaining 2 patients (no. 18 and 20) were more severely ill. Patient no. 18 was severely cyanotic and was in congestive failure during the month prior to operation; patient no. 20 had spells of severe dyspnea with increase of the cyanosis.

Postoperatively these latter 2 patients have shown great improvement and are now active and without symptoms. All patients who were symptomatic prior to surgery have reported an increase in their exercise tolerance.

It is worth re-emphasizing[12] that symptomatology plays only a minor role in the evaluation of patients for operation, as symptoms occur late in the course of the natural history of this anomaly, and patients with severe stenosis may be relatively asymptomatic.

Electrocardiographic Observations

All patients showed a degree of right ventricular hypertrophy preoperatively. Postoperatively various degrees of regression of the pattern of right ventricular hypertrophy have been observed depending upon the period of observation. All patients who were observed for a period of at least 6 months have revealed a decrease in the height of the R wave in leads V_3R, V_1, and aV_R, and in the depth of the S wave in V_6 and V_7. In 5 patients the tall upright deflection present in leads V_3R and V_1 changed to an rSR′ pattern. This pattern has been frequently interpreted as indicating incomplete right bundle-branch block. However, a QRS duration of only .08 to .10 second in the presence of an rSR′ complex is considered to reflect minimal hypertrophy of the right ventricle mainly in the structures of the outflow tract (figs. 1 and 2).[13] It is expected that

with further regression of the hypertrophy a normal electrocardiographic pattern will develop.

Radiography

There was roentgenologic evidence of significant preoperative cardiac enlargement in only 1 patient in this series (no. 18); this patient was in failure at that time. Although there is enlargement of the right atrium and hypertrophy of the right ventricle, the over-all heart size may be within normal limits despite the presence of severe pulmonary valvular stenosis.

Thus, until dilatation and failure of the heart supervene, the over-all heart size may be within normal limits or only slightly enlarged. There was a reduction in heart size in patient no. 18. There was no significant reduction in heart size in the other patients; to the contrary, a slight increase in over-all heart size following surgery was detected in 10 patients. This increase was minimal and occurred in the immediate postoperative period. The heart size has not increased further in any of these patients, and is considered to be within normal limits at the present time.

Preoperatively the vascularity of the lung fields was considered to be within normal limits in all 15 patients with an intact atrial septum. This observation is in agreement with the hemodynamic observation that the pulmonary blood flow at rest is normal in volume and equal to the peripheral systemic blood flow in these patients despite the stenosis of the pulmonary artery. Postoperatively the vascularity did not change in these patients.

The vascularity of the lung fields appeared decreased in the cyanotic patients; particularly the periphery of the lung fields appeared more translucent than normal. Postoperatively an increase in the pulmonary vascularity was noted in at least 3 of these patients; in the others no definite change has been observed.

Patient no. 24 demonstrated a slightly increased vascularity of the lung fields prior to valvuloplasty. After this operation the vascularity increased considerably; at the present time, however, 20 months following closure of the atrial septal defect, the vascularity of the lung fields is considered to be within normal limits.

Hemodynamic Observations

In 14 patients the preoperative systolic pressure gradient across the pulmonary valve was greater than 100 mm. Hg and in 5 patients it was over 150 mm. Hg. Following surgery the systolic pressure gradient between the right ventricle and pulmonary artery was markedly decreased or completely obliterated in 17 of the 25 patients. We have arbitrarily chosen a gradient of 20 mm. Hg or less as indicative of an ideal result and of the absence of significant residual stenosis. It is with the remaining 8 patients that we are particularly interested. Four of these had residual pressure gradients greater than 30 mm. Hg, the greatest being 59 mm. Hg.

There are several explanations that may be considered in regard to this residual gradient. The first possibility is that the stenosis was inadequately relieved at the time of the surgical procedure. This is considered unlikely for the following reasons. The surgical procedure was performed under direct vision in a bloodless field. The valve was incised from its central aperture down to the annulus, along the lines of the commissures, whenever they were present. When only rudimentary commissures were noted at the base of the valve, the incisions were made from the aperture of the valve to these sites. Following this procedure in all adults and in all children with a pulmonary artery of sufficient size, the surgeon introduced a finger through the valve and palpated the subvalvular area. In patients in whom the size of the pulmonary artery did not allow this maneuver, a surgical clamp was passed through the valve orifice and spread, revealing that the valve had been opened to the limits of the annulus. The subvalvular area was also probed for additional sites of obstruction.

A second consideration is that some valve cusps, being fibrosed, were sufficiently rigid to obstruct blood flow although adequate incisions had been made. This possibility exists but is difficult to evaluate.

A third explanation for a residual pressure gradient is the presence of an anatomic infundibular stenosis. At the time of operation in all patients the surgeon explored the subvalvular area with his finger or with an instrument. No evidence of an infundibular stenosis was found; however it remains possible that an infundibular stenosis was present lower in the ventricle.

There is one additional explanation that might account for this residual gradient: marked hypertrophy in the area of the crista supraventricularis and other structures forming the right ventricular outflow tract[14, 15] may act as an obstruction to the flow of blood into the pulmonary artery. If the residual gradient is chiefly the result of the obstruction offered by the hypertrophied outflow tract, then it is anticipated that this gradient will decrease with regression of the hypertrophy. A definite answer will not be forthcoming until more patients are restudied at longer intervals following surgery. However, in one patient (no. 21) who was catheterized on 2 occasions following surgery, the first time in the immediate postoperative period and the second time a year following surgery, the findings may be interpreted as supporting the hypothesis that the hypertrophied outflow tract of the right ventricle may be the cause of the presence of a residual gradient in some patients (table 2).

This patient (no. 21), was a 13-year-old cyanotic girl in whom a Blalock-Taussig procedure had been performed at the age of 5. This anastomosis thrombosed shortly after the operation, and little change was noted in the patient's clinical condition. At age 8 a transventricular valvulotomy by the Brock technic was performed. Prior to the latter operation the right ventricular pressure was 190/8 mm. Hg, the pressure in the pulmonary artery was 18/10 mm. Hg, and the femoral arterial blood oxygen saturation was 78 per cent. Recatheterization in February 1955 revealed the pressure in the right ventricle to be 120/5 mm. Hg; the femoral arterial blood oxygen saturation was 80 per cent. At the third operation in Denver in June 1955, a long, conical valve with an orifice of 4 mm. in diameter was observed. Three incisions were made down to the valve ring along the lines of the commissures and the surgeon inserted his finger through the valve into the outflow tract of the right ventricle. The outflow tract was narrowed presumably as a result of the severe hypertrophy of the ventricle. No definite sites of infundibular stenosis were considered to be present. The valve leaflets were pliable.

Two weeks later the right ventricular pressure was 60/3 mm. Hg and the pulmonary artery pressure was 28/16 mm. Hg. On withdrawal of the catheter the pressure tracing showed an intermediate pressure zone between the pulmonary artery and the right ventricle (fig. 5). Thus, on withdrawing into the subvalvular area, the systolic pressure remained at the same level as in the pulmonary artery while the diastolic pressure fell to a level of 5 mm. Hg. On continued withdrawal into the lower right ventricle the systolic pressure suddenly rose to 60 mm. Hg. Prior to surgery there was no evidence in the withdrawal pressure tracing of an infundibular chamber. The immediate postoperative electrocardiograms were not significantly different from the preoperative tracings, continuing to reveal marked

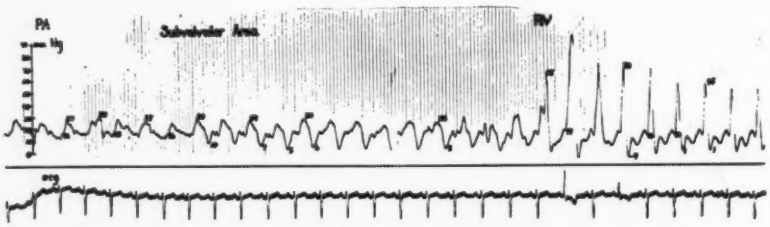


FIG. 5. Pressure tracing obtained on withdrawing cardiac catheter shortly after the third operation in patient 21, showing an intermediate pressure zone between the pulmonary artery and right ventricle.

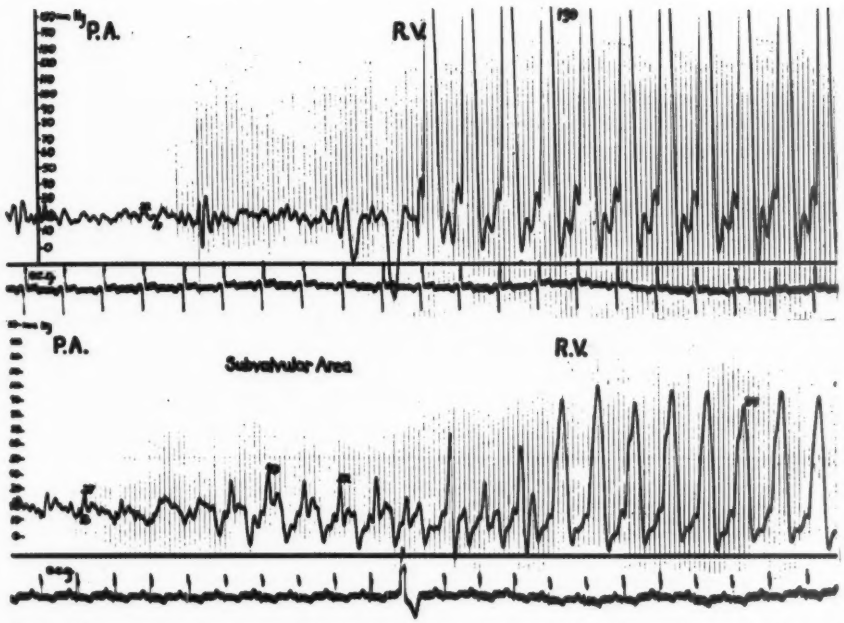


FIG. 6. Pressure tracings at catheterization before (*top*) and after (*bottom*) operation in patient 10, showing postoperatively an intermediate subvalvular pressure area.

right ventricular hypertrophy (fig. 2). The peripheral arterial blood oxygen saturation was 73.6 per cent.

Recatheterization in May 1956, 11 months following the last operation, demonstrated a pulmonary artery pressure of 23/13 mm. Hg, a right ventricular pressure of 45/8 mm. Hg, and the continued evidence in the withdrawal pressure tracing of an infundibular chamber with a pressure of 30/8 mm. Hg.* The peripheral arterial oxygen saturation was 91 per cent, which represents a significant increase over the previous values. At this time the electrocardiogram showed a striking change, with evidence of marked regression of the right ventricular hypertrophy (fig. 2).

A second patient (no. 10) also revealed changes in the postoperative withdrawal pressure tracing that suggested the presence of an intermediate pressure zone (fig. 6). Preoperatively the pulmonary artery pressure was 25/13 mm. Hg, with an abrupt change to a right ventricular systolic pressure of 190 mm. Hg. This change occurred high at the level of the pulmonary valve. The peripheral arterial saturation was 93.2 per cent. At operation the valve appeared conical with an orifice 4 to 5 mm. in diameter. The lines of the fused commissures were visible and the valve was incised along these 3 lines to the annulus. Recatheterization 10 days postoperatively revealed a right ventricular pressure of 85/10 mm. Hg and a pulmonary arterial pressure of 28/10 mm. Hg. The withdrawal pressure tracing at this time revealed a pressure tracing suggestive of an intermediate chamber (fig. 6): in the immediate subvalvular area there was a slight rise in the systolic pressure and a fall of the diastolic pressure to zero; on further withdrawal there was an additional abrupt rise in the systolic pressure level to 85 to 90 mm. Hg.

Although both patients (no. 10 and 21) were not considered to have an anatomic infundibular stenosis preoperatively and showed an abrupt transition in their withdrawal tracings without evidence of an intermediate pressure

* We are greatly indebted to Professor P. Soulié for his kindness in sending to us the results of his studies on this patient and for his permission to include these data in this paper.

zone, their postoperative pressure records have revealed a wave form commonly considered suggestive of infundibular stenosis. The explanation is offered that preoperatively these patients had 2 sites of obstruction in series. The distal one, being the more severe, obscured the presence of the less significant proximal obstruction. Following removal of the distal obstruction of the valvular stenosis, however, the proximal obstruction due to the hypertrophied outflow tract became manifest. The pressure tracing noted in these 2 patients postoperatively is considered to reflect obstruction to blood flow by the structures of the hypertrophied outflow tract of the right ventricle, which developed as a result of the valvular stenosis.

A true anatomic infundibular stenosis must of course be considered in some cases. However this does not appear to be the case in patient no. 21 in view of the continued fall in the right ventricle systolic pressure level attending the regression of the right ventricular hypertrophy.

Postoperative Pulmonary Hypertension

Slight to moderate pulmonary hypertension was encountered postoperatively in 6 patients (no. 8, 11, 12, in table 1; and 19, 23, and 25, in table 2), although the pulmonary artery pressures were normal preoperatively. Exercise resulted in an additional increase in the pulmonary artery pressure in patient no. 8 (to 64/29 mm. Hg) and in patient no. 12 (to 59/43 mm. Hg). The pulmonary artery pressure during exercise was not recorded postoperatively in the remaining 4 patients. In one additional patient pulmonary hypertension was manifest only during exercise.

The explanation for the development of the postoperative hypertension in these patients is not evident. It might be considered to reflect an increase in the pulmonary artery blood flow in the face of minimal structural changes in the pulmonary vessels. However, there is no definite evidence to support this supposition. The pulmonary artery blood flow at rest has not increased significantly in any of these patients, and, as to the possibility of structural changes, no pulmonary biopsy specimens were obtained.

Multiple thromboses with recanalization have been observed by Rich[16] in the pulmonary vessels of patients with a tetralogy of Fallot. Recently this subject has been reviewed by Dammann and Ferencz[17] and it was found that the small pulmonary arteries in patients with pulmonary stenosis were thin walled with wide lumens and could not be distinguished from those found in normal lungs. Lung sections obtained from patients of an older age group, however, frequently revealed pulmonary arteries containing thrombi similar to those described by Rich.[16] These changes were thought to be the results of polycythemia, hypoxia, and inadequate pulmonary blood flow due to the pulmonary stenosis. However none of the patients with postoperative pulmonary hypertension was polycythemic; slight peripheral arterial oxygen unsaturation was present in only 3 (patients 19, 23, and 25, table 2), while the pulmonary arterial oxygen saturation varied between 52 and 72 per cent. Only the 1 patient (no. 6) with a normal resting pulmonary artery pressure and a rise above normal during exercise demonstrated a very low (38 per cent) oxygen saturation of the pulmonary artery blood. Therefore it seems unlikely that the postoperative hypertension was the result of hypoxia.

A definite explanation for this postoperative phenomenon must therefore await further investigation.

Evaluation of Surgical Therapy

Patients with valvular pulmonary stenosis have been divided into 2 groups on the basis of the presence or absence of an associated defect in the atrial septum.

We are satisfied at the present time that the procedure of choice in patients with an intact atrial septum is the direct approach to the stenotic valve through an incision in the pulmonary artery. However, in the patients in whom there is an associated defect in the atrial septum, the surgical approach is not so evident. In the patients with a left-to-right shunt through the defect, it is considered that the atrial septal defect should be closed first, and the pulmonary stenosis should be relieved at the same operation if the condition of the pa-

tient permits. Should the condition of the patient not warrant it, then pulmonary valvuloplasty can be performed at a later date.

The reason for this sequence has been demonstrated by the course of patient no. 24, in whom removal of the pulmonary stenosis was followed by increased left-to-right shunt and congestive failure. This patient slowly responded to medical therapy and closure of the atrial septal defect was accomplished 6 months later. At the present time her heart size has decreased to normal and she is asymptomatic.

The problem of the surgical approach is different in patients with a right-to-left shunt through the defect in the atrial septum. If the defect is small and due to a foramen ovale, closure may occur following surgery. The relief of the pulmonary stenosis and subsequent regression of the hypertrophy of the right ventricle will result in a decrease in the right atrial pressure. The re-establishment of the normal relationship between the right and left atrial pressures then might result in closure of the foramen ovale. This apparently has occurred in 2 patients, (no. 17 and 21) in whom there has been a marked regression of the hypertrophy of the right ventricle, as reflected by the electrocardiogram and the complete or nearly complete obliteration of the right-to-left shunt. When the flow of blood is from right to left through the defect in the atrial septum, then it is considered that the stenosis of the pulmonary valve should be relieved first in contrast to the order of repair in patients with a left-to-right shunt. The indications for closing the defect in the atrial septum at the time of valvuloplasty are not clearly established. At the present time it is our plan to open the right atrium following relief of the pulmonary stenosis, and if the defect in the atrial septum appears to be of considerable size and if the patient's condition permits, the defect will be closed. However, should the defect feel small and if there is considered to be a velum, such as to suggest dilatation of a foramen ovale, then further surgery will be postponed.

Summary

Clinical and physiologic studies have been carried out in 25 patients following surgical correction of congenital valvular pulmonary stenosis. The patients were operated upon under conditions of hypothermia and circulatory occlusion, permitting plastic repair of the stenotic pulmonary valve with unimpaired vision and a dry operative field. The results are considered to be superior to those obtained with the blind transventricular approach. The operative mortality certainly compares favorably with the transventricular approach. Auscultatory evidence of insufficiency of the pulmonary valve is occasionally noted; however, it is emphasized that no valvular substance has been excised in the last 35 patients. The first 3 patients, who have been previously reported,[1] have now been followed for a period of 3½ years and there has been no clinical nor physiologic evidence that this minimal degree of pulmonary insufficiency is significant.

The systolic pressure gradient between the right ventricle and the pulmonary artery has been completely abolished in 17 of the 25 patients. A residual pressure gradient of more than 20 mm. Hg was present in 8 patients. Possible explanations for the residual pressure gradient are presented.

Finally, the recording of pulmonary hypertension has been reported following relief of the pulmonary stenosis and explanations for this are considered.

Summario in Interlingua

Studios clinic e physiologic ha essite executate in 25 patientes post correction chirurgic de congenite stenosis del valvula pulmonar. Le operationes esseva effectuate sub conditiones de hypothermia e occlusion circulatori de maniera que le reparo del stenotic valvula pulmonar poteva facer se con visualisation complete in un non-inundate campo chirurgic. Le resultatos obtenite es considerate como superior a illos possibile per le occulte methodo transventricular. Isto es clarmente evidente ab un comparation del procentages de mortalitate. Indicios auscultatori de insufficientia del valvula pulmonar es a vices a notar, sed le autores sublinea le facto que nulle excision de substantia valvular esseva effectuate in le ultime 35 patientes de lor serie. Le prime 3 pa-

tientes, reportate in un previe publication, ha nunc essite sub observation post-operatori durante un periodo de 3½ annos, e nulle indication clinic o physiologic existe a suggerer que iste grado minimal de insufficientia pulmonar es significative.

Le gradiente de pression systolic inter le ventriculo dextere e le arteria pulmonar esseva completemente abolite in 17 del 35 patientes. Un residuo de gradiente de plus que 20 mm Hg persisteva in 8 casos. Es presentate explicationes possibile del residue gradiente de pression.

Es reportate, finalmente, le registration de hypertension pulmonar post alleviamento del stenosis pulmonar. Explicationes es considerate.

REFERENCES

[1] Blount, S. G., Jr., McCord, M. C., Mueller, H., and Swan, H.: Isolated valvular pulmonic stenosis. Clinical and physiologic response to open valvuloplasty. Circulation **10:** 161, 1954.

[2] Campbell, M., and Brock, R. C.: The results of valvulotomy for simple pulmonary stenosis. Brit. Heart J. **17:** 229, 1955.

[3] Hosier, D. M., Pitts, J. L., and Taussig, H. B.: Results of valvulotomy for valvular pulmonary stenosis with intact ventricular septum. Abstr. of papers, Second World Congress of Cardiology, 1954, p. 382.

[4] Lillehei, C. W., Winchell, P., Adams, P., Baronofsky, I., Adams, F., and Varco, R. L.: Pulmonary valvular stenosis with intact ventricular septum. Am. J. Med. **20:** 756, 1956.

[5] Silverman, B. K., Nadas, A. S., Wittenborg, M. H., Goodale, W. T., and Gross, R. E.: Pulmonary stenosis with intact ventricular septum. Correlation of clinical and physiologic data, with review of operative results. Am. J. Med. **20:** 53, 1956.

[6] Swan, H., Cleveland, H. C., Mueller, H., and Blount, S. G., Jr.: Pulmonic valvular stenosis. J. Thorac. Surg. **28:** 504, 1954.

[7] Ellison, R. G., Brown, W. J., Hague, E. E., Jr., and Hamilton, W. F.: Physiologic observations in experimental pulmonary insufficiency. J. Thorac. Surg. **30:** 633, 1955.

[8] Fowler, N. O., Mannix, E. P., and Noble, W.: Some effects of partial pulmonary valvectomy. Circulation Research **4:** 8, 1956.

[9] Gerbode, F., Ratcliffe, J., Hurt, R., and Melmonte, B.: The physiological response to total excision of the pulmonary valves: an experimental study. Presented at meeting of Society for Vascular Research, Chicago, June, 1956.

[10] Swan, H. Unpublished data.

[11] Kay, J. H., and Thomas, V.: Experimental production of pulmonary insufficiency. Arch. Surg. **69:** 646, 1954.

[12] Blount, S. G., Jr., Komesu, S., and McCord, M. C.: Asymptomatic isolated valvular pulmonary stenosis. New England J. Med. **248:** 5, 1953.

[13] —, Munyan, E. A., and Hoffman, M. S.: Hypertrophy of the outflow tract of the right ventricle: A concept of the electrocardiographic findings in atrial septal defects. Am. J. Med. In press.

[14] Kirklin, J. W., Connolly, D. C., Ellis, F. H., Burchell, H. B., Edwards, J. E., and Wood, E. H.: Problems in the diagnosis and surgical treatment of pulmonic stenosis with intact ventricular septum. Circulation **8:** 849, 1953.

[15] Bing, R. J., Reber, W., Sparks, J. E., Balboni, F. A., Vitale, A. G., and Hanlon, M.: Congenital pulmonary stenosis. J. A. M. A. **154:** 127, 1954.

[16] Rich, A. R.: A hitherto unrecognized tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (tetralogy of Fallot). Bull. Johns Hopkins Hosp. **82:** 389, 1948.

[17] Dammann, J. F., Jr., and Ferencz, C.: The significance of the pulmonary vascular bed in congenital heart disease. Am. Heart J. **52:** 7, 1956.

Science increases our power in proportion as it lowers our pride.—Claude Bernard, 1813–1878.

Aging of Arteries in Relation to Hypertension

By James Conway, M.D., Ph.D., and K. Shirley Smith, M.D., F.R.C.P.

With a new clinical test for the assessment of the elastic quality of the arterial reservoir, evidence has been obtained suggesting that essential hypertension can be separated into 2 distinct clinical types. In one group the elevation of pressure appears to be the consequence of physiologic aging of arteries and in the other hypertension is imposed upon a normal elastic arterial system. Patients in the elastic group were younger and had a more severe type of hypertension than those in the inelastic group.

THE most important changes in the arterial tree with age are loss of elasticity and the development of variable amounts of atherosclerosis. The former is the more characteristic and uniform change, and it is this aspect of aging that is to be considered here. The increasing rigidity of arteries is responsible for the increase in pulse pressure with age, a relationship that was recorded in the earliest measurements of blood pressure in the population[1] and recently it has been studied more closely by Master, Marks, and Dack[2] and Russek and Zohman,[3] in America, and by Hamilton, Pickering, Roberts, and Sowry[4] in England. From the normal trend of a rising blood pressure with age, Pickering[5] has made a strong plea for regarding essential hypertension as an exaggerated manifestation of the normal aging process. This concept is vital to the understanding of the nature of hypertensive disease and it suggests that the causative mechanism should be sought in the population at large and not as an extrinsic morbid process.

The objective of the present work is to obtain evidence to show whether hypertension is a natural accompaniment of the aging of arteries or whether it is caused by pressor mechanisms acting upon a normally elastic arterial system. Some additional data will also be provided concerning the possibilities that hypertension may lead to premature aging of arteries or, by stretching, make them appear to be more rigid than they normally are.

A clinical method has been developed[6] by which it is possible to assess the elastic qualities of the great vessels in man. The test depends upon changes in pulse pressure that occur when the diastolic pressure is reduced without significant changes in stroke volume. It has been assumed that this can be achieved for a limited number of heart beats immediately after the inhalation of amyl nitrite, when for a few cycles, the blood pressure falls without change in heart rate. Although this test is crude and indirect, we believe that it is capable of achieving the objectives of this work.

Methods and Material

The test was conducted with the subject lying supine upon a couch with enough support to the head for comfort. No premedication was given but all the patients were seen beforehand and told of the nature of the procedure. After infiltration of the skin over the brachial artery with 2 per cent procaine or lignocaine, a short-beveled needle (no. 25) was inserted into the brachial artery, and connected by a short piece of polythene tubing (20 cm. long with an internal bore of 0.5 or 1 mm.) to the condenser manometer. The natural frequency of the saline-filled manometer, connecting tubing and needle was approximately 20 cycles per second. The manometer was calibrated against known static pressures before use and checked at intervals during the investigation. The needle was frequently flushed with heparinized saline to prevent the accumulation of blood clot at the tip of the needle. Records were made photographically with mirror galvanometers or with ink-writing oscillographs; for accuracy in the measurement of the pulse pressure the output from the amplifier was arranged to give the greatest possible deflection for each instrument while allowing an adequate margin for changes in pressure level. A time record was included and wherever possible the electrocardiogram and respiration were also recorded.

After the initial blood pressure had been recorded, a crushed phial or container of amyl nitrite was held under the subject's nose for 1 or 2 breaths and the blood pressure record was continued to show the fall

From Charing Cross Hospital, London, England.

For the development of the method used in this work one of us (J. C.) was given a Ciba Foundation Award for research on aging in 1956.

and return of pressure to normal. In the measurement of pulse pressure trends, particular care was taken to compare equivalent beats with respect to heart rate and respiration before and after the onset of the depressor effect of amyl nitrite. The change in pulse pressure in the 3 heart beats immediately preceding the onset of tachycardia has been expressed as a percentage of the simultaneous fall in diastolic pressure.

In many subjects the test was repeated on more than 1 occasion at a single session and in 5 subjects the test was repeated on a second occasion. The test was also repeated in some subjects after the administration of hexamethonium dibromide (10 to 30 mg. intravenously) or tetraethylammonium bromide (300 to 500 mg. intravenously). Since this ganglion blockade affected the initial level of blood pressure, comparisons between normal subjects and those with hypertension have been drawn from tests performed without hexamethonium. Changes in the response produced by ganglion blockade will be mentioned separately.

The test has been performed on 16 normal young subjects and an unselected group of 52 patients admitted to Charing Cross Hospital for the investigation and treatment of hypertension. The admission of patients to the hospital and their care and investigation were under the control of several physicians attending the hospital. At the time that this work was being done they knew the nature of the tests being performed on their patients but nothing of the results and their possible practical application. The clinical data of these cases were therefore obtained entirely independently of the present work, and the group was representative of the types of patient with hypertensive disease referred to consultant physicians by general practitioners. A small number of patients were admitted to the hospital directly from the casualty department. At the time of the test no specific hypotensive treatment was being administered.

In recording the diagnoses of these patients, a renal cause had been presumed to be present if there was any evidence of renal disease, either in the past history or in the function tests. Hypertension appearing in pregnancy was considered to be of renal origin. Patients with clinical evidence of heart failure were excluded from this investigation.

Results

Response of Normal Subjects

The age of the normal subjects ranged from 17 to 32 years, with an average of 24 years. Their average initial blood pressure was 124 mm. Hg systolic, and 72 mm. Hg diastolic, with an average heart rate of 79 beats per minute (table 1). In the 50 tests performed on these subjects the average reduction in diastolic pressure before reflex tachycardia emerged was 11 mm. Hg and the concomitant fall in pulse pressure was only 15 per cent (S.D. 18.8) of the fall in diastolic pressure (fig. 1).

TABLE 1.—*Initial Blood Pressure of Normal Subjects and Effect of Amyl Nitrite on Pulse Pressure*

Sex and age (yr.)	Initial data			Change in pulse pressure as percentage of fall in diastolic pressure
	Diastolic pressure mm. Hg	Pulse pressure mm. Hg	Rate (beats/min.)	
M, 26	70	40	68	0
F, 30	85	45	83	33
M, 27	80	45	62	6
M, 27	60	50	60	6
M, 21	55	75	90	38
M, 23	75	50	90	53
F, 22	70	45	70	18
M, 17	85	40	80	50
F, 20	75	50	102	9
F, 32	75	30	70	10
M, 25	75	80	70	9*
M, 22	60	60	90	9
M, 20	65	65	80	7
M, 22	75	55	104	0
M, 23	65	55	54	7*
M, 24	75	45	83	18
Average 24	72	52	79	15
(S.D.) (3.9)	(8.7)	(13.0)		(18.8)

* In 2 subjects there was an increase in pulse pressure as the diastolic pressure fell after amyl nitrite.

Limits of the normal response were established from the data of these normal young subjects. The range given by twice the standard deviation would include 95 per cent of all observations. The upper limit of the normality would therefore be 52.6 per cent, and for convenience this was rounded off to 55 per cent. When the test was repeated after the administration of hexamethonium in 7 of these subjects, the level of diastolic pressure had fallen by 9 mm. Hg, but the change in pulse pressure was again quite small—20 per cent of the change in diastolic pressure.

Hypertensive Patients

The level of blood pressure used in this study has been the one found by direct arterial puncture at the time of the test. It was appreciated that patients could not be considered to be

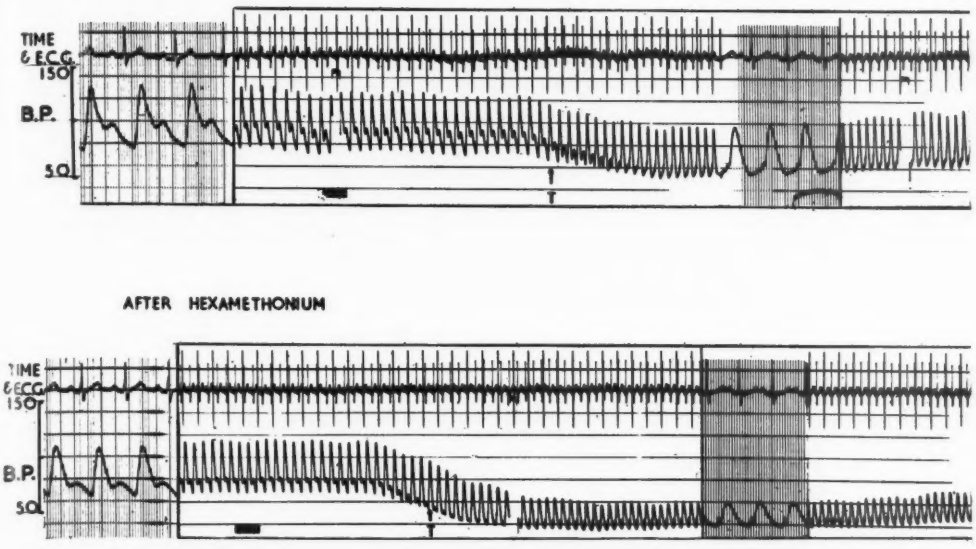


FIG. 1. Effect of amyl nitrite on the blood pressure, before and after hexamethonium, in a normal young subject (male, 24 years old). A time-tracing at 1 per second was run with the electrocardiogram. Gaps in the pressure record occurred as the needle in the brachial artery was being flushed through with heparinized saline. *T* indicated the onset of reflex tachycardia. The approximate time of inhalation of amyl nitrite was indicated by a signal below the pressure tracing. In this record small sections of tracing at a faster paper-speed have been inserted to illustrate the effect of amyl nitrite on the contour of the pulse wave. At the faster paper speed the timing lines are those of the conventional electrocardiogram.

"at rest" in the atmosphere of the laboratory, but in only 10 patients did the heart rate exceed 100 beats per minute and the direct readings of the blood pressure were nearly always lower than those recorded by indirect means in the wards.

It so happened that in this group of hypertensive patients there were 15 who were clearly suffering from systolic or arteriosclerotic hypertension, the diastolic pressure being 100 mm. Hg or less and the pulse pressure equal to or exceeding the diastolic pressure. With evidence of extensive arteriosclerosis they formed a useful group for the investigation of the theoretical basis of the test.

Arteriosclerotic Hypertensive Patients. The average age of these patients was 61 years, and the average pressures were 208 mm. Hg systolic and 93 mm. Hg diastolic. The heart rate averaged 76 beats per minute (table 2). In 30 tests performed on this group the average reduction in pulse pressure before tachycardia appeared was 116 per cent (S.D. 29.1) of the fall in diastolic pressure.

The range of this response, given by twice the standard deviation gave a lower limit for the change in pulse pressure of 58 per cent of the fall in diastolic pressure. Thus there was practically no overlap in the distribution of the observations in normal subjects and patients with marked clinical arteriosclerosis; the statistical significance of this difference was of course very high ($t = 12, p < 0.001$). Hexamethonium, which was given to 8 patients in this group, produced an average reduction in diastolic pressure of 30 mm. Hg. Repetition of the test at this lower level of pressure gave an average fall in pulse pressure of 124 per cent.

It seemed, therefore, that the theoretical basis of the test was upheld in practice and the remaining 37 patients, in whom clinical observation could not indicate the state of the main arteries, have been grouped according to their responses to the elasticity test.

TABLE 2.—*Initial Blood Pressure of Patients with Arteriosclerotic Hypertension, and Effect of Amyl Nitrite on Pulse Pressure*

Sex and age (yr.)	Initial data: Diastolic pressure mm. Hg	Initial data: Pulse pressure mm. Hg	Initial data: Rate (beats/min.)	Change in pulse pressure as a percentage of fall in diastolic pressure
M, 73	100	100	60	118
F, 47	100	120	78	143
F, 68	100	150	90	110
F, 51	100	135	60	128
M, 56	100	120	80	88
F, 60	95	105	98	122
F, 68	95	120	72	99
F, 56	90	90	100	86
F, 60	90	150	70	129
F, 63	85	120	60	135
M, 65	90	105	64	75
F, 63	80	95	70	164
F, 64	85	135	76	77
F, 58	100	100	80	107
F, 61	85	85	80	162
Average 61	93	115	76	116
(S.D.) (6.7)	(7.0)	(20.5)		(29.1)

Elastic Group of Hypertensive Patients. This group contained 20 patients in whom the response to the test was within the limits for the young normal subjects, and it was therefore believed that they had normally elastic arteries. The average age of these patients was 47 years, while the pressure averaged 226 mm. Hg, systolic and 130 mm. Hg diastolic. The average heart rate was 86 beats per minute (table 3). Thirty-three tests were performed on patients in this group, with an average reduction in pulse pressure of 28 per cent (S.D. 19.1) of the fall in diastolic pressure. This was 13 per cent greater than the average response of the normal young subjects and the difference was significant at the 1 in 20 level ($t = 2.05$).

Hexamethonium was given to 10 patients in this group. It produced an average reduction of diastolic pressure by 29 mm. Hg. Repetition of the test thereafter gave an average reduction in pulse pressure of 41 per cent (S.D. 19.7) of the fall in diastolic pressure. This increase in the response was largely due to 1 patient and the difference between the average responses to the test before and after hexamethonium was not significant ($t = 1.8$, $p < 0.1 > 0.05$).

TABLE 3.—*Initial Blood Pressure of Patients with the "Elastic" Type of Hypertension, and Effect of Amyl Nitrite on Pulse Pressure*

Sex and age (yr.)	Initial data: Diastolic pressure mm. Hg	Initial data: Pulse pressure mm. Hg	Initial data: Rate (beats/min.)	Change in pulse pressure as a percentage of fall in diastolic pressure
M, 38	150	60	61	41
F, 58	150	90	76	25
M, 49	130	75	68	37
M, 58	170	100	118	0
M, 47	150	120	86	23
F, 49	140	110	80	18*
M, 38	115	70	84	33
M, 49	110	110	80	38
F, 54	150	140	105	0
F, 39	140	70	90	52
F, 59	150	135	100	49
M, 34	110	75	66	20
F, 26	140	85	100	34
M, 52	140	105	92	19
M, 45	140	140	104	13*
F, 38	110	65	80	53
M, 35	100	80	85	31
F, 59	95	95	75	55
M, 52	115	110	86	28
F, 60	100	80	90	52
Average 47	130	96	86	28
(S.D.) (9.9)	(21.5)	(24.9)		(19.1)

* In 2 patients there was an increase in pulse pressure as the diastolic pressure fell after amyl nitrite.

Inelastic Group of Hypertensive Patients. The remaining 17 patients with hypertension showed a considerable reduction in pulse pressure after amyl nitrite. They were therefore believed to have inelastic arteries. Their average age was 56 years. The systolic pressure averaged 234 mm. Hg and the diastolic pressure 113 mm. Hg, the heart rate being 84 beats per minute (table 4). In 25 tests performed on these patients, the average reduction in diastolic pressure was 96 per cent (S.D. 30.3) of the simultaneous fall in diastolic pressure.

Hexamethonium was given to 5 patients in this group reducing the diastolic pressure by 24 mm. Hg and thereby also reducing the average change in pulse pressure after amyl nitrite to 74 per cent of the fall in diastolic pressure. The numbers of patients tested in this way was too small to enable firm conclu-

TABLE 4.—*Initial Blood Pressure of Patients with the "Inelastic" Type of Hypertension, and Effect of Amyl Nitrite on Pulse Pressure*

Sex and age (yr.)	Initial data			Change in pulse pressure as a percentage of fall in diastolic pressure
	Diastolic pressure mm. Hg	Pulse pressure mm. Hg	Rate (beats/min.)	
F, 59	115	105	68	71
F, 67	120	100	114	73
F, 54	115	65	92	71
F, 56	105	105	92	112
F, 61	115	125	70	100
M, 60	130	140	68	75
M, 49	120	130	120	61
M, 50	100	95	78	64
F, 53	130	130	64	125
M, 60	110	105	78	93
M, 62	105	115	68	66
F, 54	105	95	108	127
M, 48	110	110	74	127
F, 47	120	155	110	93
F, 57	105	185	60	157
F, 55	110	120	64	108
M, 60	110	175	105	111
Average 56	113	121	84	96
(S.D.) (6.5)	(8.6)	(30.2)		(30.3)

sions to be drawn from this trend but it was of particular interest that in 3 of 5 patients tested the reduction in diastolic pressure converted the "inelastic" type of response to the "elastic" or normal type. This was of considerable theoretical importance. This reversion to normality was not seen in any patients in the arteriosclerotic group after reducing the blood pressure with hexamethonium.

Characteristics of the Different Types of Hypertension. The difference of 68 per cent in the response to the test between the elastic and inelastic groups of patients was highly significant ($t = 8.3$, $p < 0.001$) but the difference between the inelastic group of hypertensive and the arteriosclerotic patients was not significant ($t = 2.0$, $p < 0.1 > 0.05$) (table 5). Similarities were evident between the inelastic and arteriosclerotic groups in other respects. They were of similar age ($t = 1.4$, $p > 0.1$) and although the initial diastolic pressure was higher in the patients of the inelastic group ($t = 7.1$, $p < 0.001$) the amplitude of pulse pressure was approximately the same ($t = 0.64$, $p > 0.10$) in the 2 groups.

In contrast, the differences between the inelastic and elastic groups were very striking. The patients of the elastic group were significantly younger than those of the inelastic group by an average of 9 years ($t = 3.3$, $p < 0.01$) and the initial pulse pressure was significantly smaller in the elastic group ($t = 2.8$, $p < 0.01$). The smaller pulse pressure was found in the elastic group in spite of a higher initial diastolic pressure; 130 mm. Hg as opposed to 113 mm. Hg in the inelastic group ($t = 3.0$, $p < 0.01$). Considerable importance has been attached to this evidence of a greater severity of the hypertension in the elastic group of patients.

These results strongly supported our belief that this test had successfully assessed the elastic quality of the arterial reservoir. The clinical characteristics of these patients suggested further that hypertension in those of the elastic group was fundamentally different from the condition in the inelastic group. Of the 20 patients of the elastic group there was an unusually large number of patients, 7, with renal hypertension (table 6) and of the 13 patients considered to have essential hyper-

TABLE 5.—*Clinical Data of Normal and Hypertensive Subjects and Effect of Amyl Nitrite on Pulse Pressure*

Subjects (no.)	Average age, years (S.D.)	Average initial blood pressure			Average initial rate (beats/min.)	Average change in pulse pressure as a percentage of the reduction in diastolic pressure (S.D.)
		Systolic mm. Hg	Diastolic mm. Hg (S.D.)	Pulse pressure mm. Hg (S.D.)		
Normal (16)	24 (3.9)	124	72 (8.7)	52	79	15% (18.8)
"Elastic" hypertensive (20)	47 (9.9)	226	130 (21.5)	96 (24.9)	86	28% (19.1)
"Inelastic" hypertensive (17)	56 (5.5)	234	113 (8.6)	121 (30.2)	84	96% (30.3)
Arteriosclerotic hypertensive (15)	61 (6.7)	208	93 (7.0)	115 (20.5)	76	116% (29.1)

TABLE 6.—*Further Clinical Characteristics of the Patients with Hypertension Grouped According to their Response in the Elasticity Test*

	Sex	Average weight (lbs.)	Main diagnosis type of hypertension				Secondary diagnosis	
			Essential		Renal			
			Benign	Malignant	Benign	Malignant	Coronary heart disease	Other
Elastic (20)	11M 9F	156	9	4	7	0	1	
Inelastic* (17)	7M 10F	141	10	2	3	1	2	Diabetes 2
Arteriosclerotic (15)	3M 12F	145	14	1	0	0	6	Diabetes 2

* One with Cushing's disease.

tension, 4 were in the malignant phase. Two of the patients with essential hypertension were treated by sympathectomy and in these the results of renal biopsy and histologic examination of the ganglionic tissue were consistent with the diagnosis of essential hypertension. One patient in this group had coronary heart disease.

In the inelastic group there were 4 patients with renal hypertension and 12 with essential hypertension; one had Cushing's disease. One of the patients with renal hypertension and 2 with essential hypertension were in the malignant phase. There were 2 instances of coronary heart disease in this group and 2 of diabetes.

All the patients of the arteriosclerotic group were considered clinically to have essential hypertension. The cause of the differences between the direct and indirect blood pressure measurement was not ascertained and is to be investigated later. One case in this group was in the malignant phase of essential hypertension, 6 suffered with coronary heart disease, and 2 with diabetes.

DISCUSSION

The responses to the test of the normal subjects and patients with arteriosclerotic hypertension, though they showed a wide individual scatter, strongly supported the theoretical basis of the test, which was further confirmed by the clinical characteristics of the patients classified into "elastic" and "inelastic" groups according to the test. The patients of the inelastic group were significantly older and had a higher pulse pressure than those of the elastic group. The clinical differences were so great as to suggest that these 2 groups of patients might, in fact, be suffering from different hypertensive diseases. This possibility appears even more likely if their initial diastolic blood pressures are considered against the normal trend of blood pressure for age and sex in the population at large. From the data of Hamilton, Pickering, Roberts and Sowry[4] the mean diastolic pressure for age and sex has been obtained and the upper limit of normality has been taken as twice the standard deviation of their observations for each age group. In all but 2 of the patients in the "elastic" group the initial diastolic pressure (fig. 2) was found to exceed the limit of the normal range of pressure for the age, and in the majority it exceeded the normal for any age. We infer that in this group a severe form of hypertension was being imposed upon a normal arterial tree. There were indeed an unusually large number of patients with renal hypertension in this group, 7 out of 20. In the absence of any definite cause for the elevation of blood pressure the remaining 13 patients were believed to have essential hypertension and in 2 of these histologic confirmation of this diagnosis was obtained. The association between hypertension and arteries of normal elasticity was first reported by Steele[7] in a group of 17 hypertensive patients without evidence of arteriosclerosis, and it is especially interesting to note that all but 3 of his patients were below 50 years of age.

In patients of the inelastic group the initial diastolic blood pressure was within the upper region of normality with the exception of 6 patients in whom the diastolic pressure was just above the normal limit (fig. 3). Hypertension in some of the patients could therefore, as suggested by Hamilton, Pickering, Roberts and Sowry,[4] be the result of the physiologic process of aging in arteries. Rigidity of arteries alone would not raise diastolic pressure and some unknown process must be responsible for an increase in peripheral resistance with age.

Hexamethonium, which lowered the blood

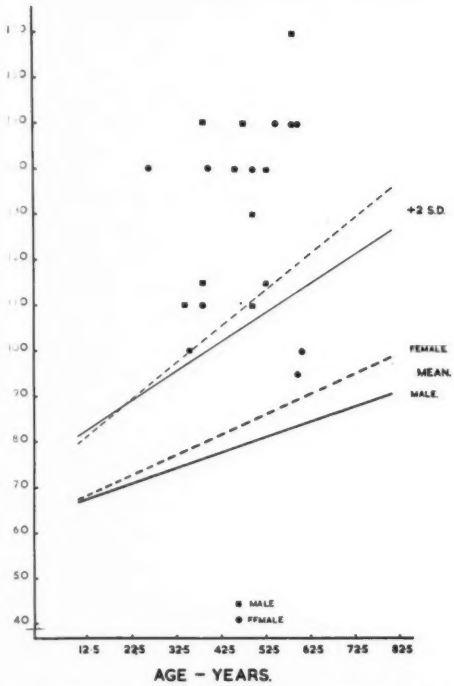


FIG. 2. The diastolic pressure (*ordinate*) of the elastic group of hypertensive patients in relation to the normal level of pressure in the general population. The mean level of diastolic pressure for age and sex and the upper limit of normality, given by twice the standard deviation of the observations for each age group in the population, are from the data of Hamilton, Pickering, Roberts, and Sowry.[4]

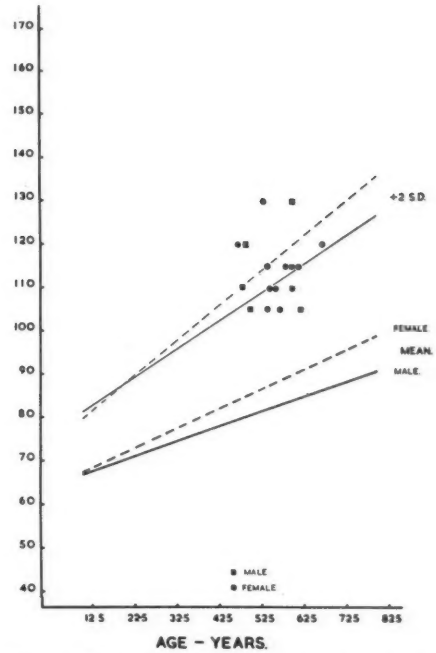


FIG. 3. The diastolic pressure (*ordinate*) of the inelastic group of hypertensive patients in relation to the normal level of pressure in the general population. (Mean and upper limits of normality as in figure 2.)

pressure, provided some subsidiary information concerning the relationship between hypertension and loss of elasticity, but the conclusions drawn from this part of the work are tentative, since the numbers of tests were small. Reducing the blood pressure in the patients with arteriosclerotic hypertension had no effect on the type of response to the test, suggesting that the sclerotic process was very advanced and affected the vessels at all levels of tension. In the inelastic group on the other hand reducing the blood pressure converted the response from the inelastic to the elastic type in 3 of the 5 patients studied. This suggested that the sclerotic process was less extensive in these subjects and that the arteries would behave as elastic vessels at lower levels of tension.

There also appeared to be some indication that hypertension could lead to aging of arteries. There were 4 patients with renal hypertension in the inelastic group, and 2 of these had an extremely long history of renal disease.

In conclusion, therefore, we consider that there is a strong case for regarding the elastic and inelastic types of hypertension as being distinct and separate diseases. The relative frequency of these 2 types of hypertensive patient in the general population is unknown but in our unselected group of patients referred to hospital for hypertension, there were, after eliminating cases of renal hypertension, equal numbers of the elastic and inelastic types. With some patients of the inelastic group the reservation must be made that loss of elasticity of the large arteries might have been the result of hypertension and not its cause. Our results therefore support the concept that aging of arteries could cause hypertension in some patients, and they suggest that the frequency of the elastic type of hypertension in the gen-

eral population would probably contribute to some distortion of the distribution curves of blood pressure for age. Since the level of pressure was so high in the patients of the elastic group, this type of hypertension would be unlikely to give a bimodal distribution curve but it could account for the positive skewness seen in the distribution curves of Hamilton, Pickering, Roberts, and Sowry,[4] and also of Master, Marks, and Dack.[2]

The difference in age and in severity of hypertension between the elastic and inelastic groups suggests that the separation of hypertension into these functional types may be of considerable clinical value and it offers some prospect of discerning the true nature of the disorder.

Summary

A clinical method has been devised for the qualitative assessment of the elastic properties of the arterial reservoir. The method depends upon changes in pulse pressure that occur after the inhalation of amyl nitrite as the blood pressure falls without change in heart rate.

The test has been applied to 16 normal young subjects and 52 patients with hypertension. In the normal subjects little change in pulse pressure accompanied the fall in diastolic pressure after amyl nitrite—15 per cent of the fall in diastolic pressure.

In the hypertensive group there were 15 patients with systolic or arteriosclerotic hypertension. In these patients the reduction in pulse pressure after amyl nitrite was 116 per cent of the simultaneous fall in diastolic pressure. The remaining patients with hypertension were grouped according to their responses to the elasticity test. In 20 patients the response was within the normal limits, and the average fall in pulse pressure was 28 per cent of the fall in diastolic pressure—these patients were believed to have normally elastic arteries. In 17 patients the fall in pulse pressure was 96 per cent of the fall in diastolic pressure and it did not differ significantly from the response of the arteriosclerotic patients. They were therefore believed to have inelastic arteries.

Clinical differences between the elastic and inelastic groups strongly suggested that these patients were in fact suffering from different diseases. The patients of the elastic group were younger and had a higher initial diastolic blood pressure than the patients of the inelastic group.

Summario in Interlingua

Esseva disveloppate un methodo pro le evalutation qualitative del proprietates elastic del reservoir arterial. Le methodo se basa super le observation de alterationes del pression pulsatile que occurre post le inhalation de nitrato de amyl quando le pression de sanguine es reducite sin alteration in le velocitate del corde.

Le test esseva usate in 16 normal subjectos de juvene etates e in 52 patientes con hypertension. In le subjectos normal, il occurreva pauc alteration del pression pulsatile quando le pression diastolic descendeva sub le effecto de nitrato de amyl: un reduction amontante a non plus que 15 pro cento del reduction del pression diastolic.

In le gruppo de hypertensivos il habeva 15 patientes con hypertension systolic o arteriosclerotic. In iste patientes le reduction del pression pulsatile post le inhalation de nitrato de amyl amontava a 116 pro cento del simultanee reduction del pression diastolic. Le resto del patientes con hypertension esseva dividite in gruppos secundo lor responsas al test de elasticitate. In 20 patientes le responsa esseva intra limites normal. Le reduction medie del pression pulsatile amontava a 28 pro cento del reduction del pression diastolic. Iste patientes esseva considerate como possedente arterias a elasticitate normal. In 17 patientes le reduction del pression pulsatile amontava a 96 pro cento del reduction del pression diastolic, i.e. le responsa in iste casos non differeva significativemente ab le responsa in le patientes arteriosclerotic. Iste gruppo esseva considerate como possedente arterias inelastic.

Differentias clinic inter le gruppo elastic e le gruppo inelastic suggereva fortemente que iste patientes suffreva de facto con differente morbos. Le patientes del gruppo elastic esseva plus juvene e habeva plus alte pressiones

diastolic initial que le patientes del gruppo in elastic.

REFERENCES

1 THAYER, W. F.: On the late effects of typhoid fever on the heart and vessels. Am. J. M. Sc. **127:** 391, 1904.

2 MASTER, A. M., MARKS, H. H., AND DACK, S.: Hypertension in people over forty. J.A.M.A. **121:** 1251, 1943.

3 RUSSEK, H. I., AND ZOHMAN, B. L.: Normal blood pressure in senescence. Geriatrics **1:** 113, 1946.

4 HAMILTON, M., PICKERING, G. W., ROBERTS, J. A. F., AND SOWRY, G. S. C.: The aetiology of essential hypertension: The arterial pressure in the general population. Clin. Sc. **13:** 11, 1954.

5 PICKERING, G. W.: High Blood Pressure. London, J. & A. Churchill, 1955.

6 CONWAY, J., AND SHIRLEY SMITH, K.: A clinical method of studying the elasticity of large arteries. Brit. Heart J. **8:** 467, 1956.

7 STEELE, J. M.: Interpretation of arterial elasticity from measurements of pulse wave velocities. Am. Heart J. **14:** 452, 1937.

Sprofkin, B. E., and Blakey, H. H.: Acute Spontaneous Cerebral Vascular Accidents in Young Normotensive Adults. Arch. Int. Med. **98:** 617 (Nov.), 1956.

Eighteen selected cases of acute spontaneous cerebral vascular accidents in young normotensive adults were reviewed. The diagnoses and subjects for discussion included disseminated lupus erythematosus, scleroderma, thromboangiitis obliterans, thrombotic thrombocytopenic purpura, fibrinogenopenia of pregnancy, postmeasles hemiplegia, subacute bacterial endocarditis, angiomatous malformation, postpartal cerebral venous thrombosis, spontaneous subcortical hematoma, and syphilis, as well as cerebral thrombosis of unknown cause. It was suggested that the precipitous decline in incidence of all forms of syphilis during the penicillin era had minimized the etiologic importance of syphilis with regard to cerebrovascular accidents in the younger age groups. The phenomenon of biologic false-positive serologic tests was discussed as a probable cause of a mistaken diagnosis of vascular syphilis. The frequency of thrombosis of the carotid arteries in young normotensive adults was emphasized. It was concluded that premature arteriosclerotic vascular changes constituted the most important pathogenetic factor in the etiology of spontaneous cerebral vascular accidents in young normotensive adults.

BERNSTEIN

Circulatory Studies in Wernicke's Encephalopathy

With Special Reference to the Occurrence of a State of High Cardiac Output and Postural Hypotension

By MICHAEL A. GRAVALLESE, JR., M.D., AND MAURICE VICTOR, M.D.

Although Wernicke's disease is clearly related to thiamine deficiency, it is rarely accompanied by the overt signs of congestive failure. There are symptoms of disordered cardiovascular function in many patients with this disease, but the relation of these symptoms to thiamine deficiency has remained undefined. In the present study, an attempt is made to define these symptoms, particularly in relation to specific treatment with thiamine. Part 1 of this study is concerned mainly with the determination of the cardiac output in 7 patients, as determined by the Evans blue dye-dilution technic; part 2 describes the postural response to tilting in 12 patients.

WERNICKE'S encephalopathy is an acute neurologic disorder characterized by ocular paralyses, nystagmus, ataxia, and mental disorder. In this country the syndrome is encountered almost exclusively in patients with chronic alcoholism; however, it is generally agreed that the role of alcohol is secondary and that the primary cause is a nutritional deficiency, specifically of thiamine.[1]

Despite the fact that the Wernicke syndrome is so clearly related to thiamine deficiency, it is rarely accompanied by overt signs of congestive heart failure. In a series of 86 patients with Wernicke's encephalopathy, only 1 manifested the advanced signs of beriberi heart disease.[2] Nevertheless, there were indications of disordered cardiovascular function in many of these patients. The history may have disclosed complaints such as postural "dizziness" or fainting, and on examination, tachycardia and minor electrocardiographic abnormalities were frequent findings. Some patients showed dyspnea on slight exertion, and a few died suddenly, the mode of death suggesting "cardiovascular collapse."

Little attention has been paid to the cardiac abnormalities of Wernicke's disease, and the relation of these abnormalities to thiamine deficiency has remained undefined. It was thought worthwhile, therefore, to study some aspects of cardiovascular function in such patients, particularly in relation to specific treatment with thiamine.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Neurology Service, Massachusetts General Hospital, and the Departments of Medicine and Neurology, Harvard Medical School, Boston, Mass.

This work was aided by a grant from the Life Insurance Medical Research Fund and by grant M767 from the National Institute of Health, U. S. Public Health Service.

MATERIALS AND METHODS

For the sake of convenience this paper is divided into 2 parts. Part 1 is concerned mainly with the determination of cardiac output (table 1) and part 2 with the postural response to tilting (table 2).

Part 1. Seven patients with acute Wernicke's encephalopathy, ranging in age from 33 to 65 years, were studied. Six of these were men. None of the patients studied had fever or signs of congestive failure. Only patients who had definite ophthalmoplegia and had received no food after admission to the hospital were included in the study. With 1 exception (AN), all the patients had the characteristic mental symptoms. Chronic alcoholism, dietary deficiency, and loss of weight and of muscle bulk were common to the entire group. One patient (JC) had Laennec's cirrhosis with edema and ascites, and 5 others had an enlarged liver or abnormal "liver function" tests. In 4 patients the tongue was red and atrophic. In 6 patients the knee and ankle jerks were depressed or absent, but there were no other signs of peripheral neuropathy. All the patients showed an ataxia of stance and gait, however, probably on a cerebellar basis. At the time the patients came under observation none showed signs of inebriation or the psychomotor signs of abstinence from alcohol.

An evaluation of the cardiovascular state was made before each study in all patients by clinical examination, fluoroscopy, estimation of venous pressure, and serial electrocardiographic tracings. X-rays of the chest were obtained periodically.

Cardiac output was determined by the Evans blue dye-dilution technic utilizing a photoelectric densimeter, as described elsewhere.[3] Oxygen consumption was measured by a 3-minute collection of expired air in a Douglas bag, the partial pressure of oxygen being measured in a Pauling Oxygen Analyzer. Standard R. Q. corrections were used in calculation.[4] Phasic and mean arterial pressures were measured directly by means of a Sanborn electromanometer. All these determinations were performed in duplicate in most instances. Peripheral vascular resistance was calculated according to the following formula[5]:

$$\frac{\text{Mean arterial pressure mm. Hg} \times 1332}{\text{Cardiac output ml./sec.}} = \text{Resistance in dynes seconds cm.}^{-5}$$

Blood pyruvic acid in cases 2 to 5 (table 1) was measured by the method of Friedemann and Haugen,[6] and blood lactic acid by the method of Barker and Summerson.[7] Normal values for fasting blood pyruvic acid concentrations ranged from 0.8 to 1.6 mg. per 100 ml. (average 1.3); for fasting lactic acid concentrations the normal values ranged from 4.7 to 12 mg. per 100 ml. of blood, (average 6.4). Cases 6 and 7 (table 1) were studied jointly with Dr. Mark D. Altschule, McLean Hospital, Waverley, Mass. Blood pyruvate and lactate in these 2 patients were determined in his laboratory by the methods of Seligson and Shapiro[8] and of Barker and Summerson[7] respectively. Normal values for pyruvic acid ranged from 0.52 to 1.32 mg. per 100 ml. (average 0.92); values for lactic acid ranged from 2.75 to 11.6 mg. per 100 ml. (average 7.4).

The original studies in each case were made after a control period of 1 to 3 days, during which time the patient was at rest in bed and had received an unfortified rice diet* as the only source of nutrition. This diet supplied the patient with about 2,000 calories daily, but was deficient in all the B vitamins. All tests, including the estimation of blood pyruvate and lactate, were done in the morning with the patients at rest and in a fasting state for at least 12 hours. Two patients were restudied 1 to 1½ hours after they had received thiamine intravenously in a dose of 100 mg. Six patients were restudied 4 to 6 days after the rice diet had been supplemented by 50 mg. of intramuscular thiamine daily.

Part 2. Postural studies were performed on 12 patients with Wernicke's encephalopathy at varying intervals in relation to treatment with thiamine (table 2). The criteria for selection of patients were the same as in part 1 of this study. The subjects consisted of 9 men and 3 women, ranging in age from 31 to 70 years; 10 of these were between 42 and 65 years. Six of the patients also served as subjects for part 1 of this study. Cardiac output studies were attempted but were unsuccessful in 4 of the remaining 6 patients.

Each subject was tested according to the following routine: At zero time the patient was placed in a supine position on a manually operated fluoroscopic table provided with a footboard and a loose leather restraining belt placed at chest level. Blood pressure was measured at approximately heart level with a standard cuff sphygmomanometer; the reading at which there was complete disappearance of sounds was taken as the diastolic pressure. Pulse rate was determined by palpation or auscultation. Control readings were made at 5-minute intervals during the first 15 minutes, and thereafter at 1-minute intervals. At 20 minutes the subject was tilted rapidly to 70° and the tilted position maintained for 5 minutes (occasionally from 10 to 30 min.). One-minute readings were continued throughout tilting and after return to the horizontal position until control levels were reestablished. Control readings of the systolic and diastolic pressures and of pulse rate were the average of the 3 stable readings just prior to tilting. During the tilt the patient was observed for evidence of pallor, sweating, and hyperactivity, and he was asked to report sensations of nausea, dizziness, faintness, or weakness.

Arbitrarily, a fall from control levels of 40 mm. Hg in systolic pressure, 30 mm. Hg diastolic, or a reduction in pulse pressure to 10 mm. Hg or less was considered to constitute an abnormal cardiovascular response to tilting.

Subjects who were tested in this way before the administration of thiamine had been kept strictly in bed; mobilization was variable during the subsequent course of treatment and testing.

Results

Clinically, none of our patients showed signs of congestive failure and in none was there an elevation of the venous pressure. One patient (JC) with advanced cirrhosis and ascites had x-ray evidence of right hydrothorax and "possible cardiac enlargement." No other case showed cardiomegaly and in most cases the heart was described as normal or small in size. The electrocardiograms were either normal or showed minor nonspecific changes (table 1). In

* This diet is the one used by Dr. Walter Kempner of Duke University. It consists of rice, fruit, fruit juices, sugar and honey, and contains the following nutrients:

Calories	2001	Iron	8 mg.
Protein	12 Gm.	Vitamin A	2,200 i.u.
Fat	1 Gm.	Ascorbic acid	115 mg.
Carbohydrate	486 Gm.	Thiamine	0.4 mg.
Calcium	0.2 Gm.	Riboflavin	0.3 mg.
Phosphorus	0.4 Gm.	Niacin	5 mg.

TABLE 1.—*Circulatory Studies in Seven Patients with Wernicke's Disease*

Patient, age, and sex	State	BSA M^2	Pulse/min.	CI	Mean CI	SI	BP(mean)	PVR	O_2 cons.	Pyruv.	Lact.	Hct.	App. time	ECG
1. JC,33,F	Untreated	1.64	102	5.4 6.0	5.7	34	125/75 (97)	830	154	—	—	33	11	—
	1 hr. after B_1	1.64	100	4.8	4.8	29	130/75 (95)	964	154	—	—	33	13	—
2. MS,57,M	Untreated	1.67	63	1.4 1.4	1.4	13	125/65 (90)	3073	142	2.1	9.3	40	22	Borderline Q-T
	1½ hr. after B_1	1.67	72	2.8	2.8	23	150/80 (105)	1794	145	—	—	—	22	
	6 days B_1	1.70	62	1.9 2.3	2.1	20	130/60 (78)	1746	126	0.8	6.9	38	21	
3. JK,65,M	Untreated	1.94	110	6.4 6.5	6.5	30	130/65 (80)	507	—	2.7	8.3	39	9	?Wolff-Parkinson-White syndrome
	5 days B_1	1.94	69	3.3 2.7	3.0	22	130/70 (85)	1167	150	1.5	5.2	38	16	S-T improvement
4. EK,42,M	Untreated	1.60	115	6.4 6.6	6.5	35	140/75 (95)	730	167	3.0	8.1	35	10.5	Borderline S-T's
	5 days B_1	1.51	107	4.0 4.4	4.2	26	165/95 (130)	1638	172	1.6	8.8	38	11	No change
	36 days B_1	1.48	125	5.0 5.5	5.3	29	180/115 (135)	1376	176	—	—	43	13	Minor changes
	Same, exercise	1.48	148	—	6.9	47	200/130 (150)	1174	505	—	—	—	8.5	
5. AN,43,M	Untreated	1.63	90	3.9	3.9	27	125/80 (100)	1258	167	2.6	16.4	38	12.5	Borderline Q-T, T's
	4 days B_1	1.62	87	3.4 4.5	4.0	28	125/85 (100)	1233	145	1.2	8.5	35	16.5	Minor improvement T's
	7 days B_1	1.65	93	4.4	4.4	29	155/105 (125)	1376	147	—	—	30	16	—
6. WB,52,M	Untreated	1.80	112	4.8	4.8	24	95/60 (73)	675	134	2.8	16.0	41	6.5	Borderline Q-T
	Same, exercise	1.80	122	—	7.2	59	110/70 (90)	555	239	—	—	41	8.5	—
	5 days B_1	1.77	59	3.0	3.0	29	155/70 (98)	1475	115	1.9	10.2	35	18	Normal
	29 days B_1	1.79	86	3.0	3.0	19	130/70 (90)	1339	142	—	—	39	8.5	Normal
7. HC,65,M	Untreated	1.66	89	1.6 2.0	1.8	12	125/68 (80)	2138	128	3.4	19.0	46	15	Borderline Q-T, nonspecific abnormality
	5 days B_1	1.66	52	1.9	1.9	22	110/55 (70)	1775	—	3.0	17.5	36	15	Ischemia pattern

All determinations done at rest except where specified "exercise." BSA = body surface area in square meters. CI = cardiac index in L./min./$M.^2$ SI = stroke output in ml./beat/$M.^2$ O_2 cons. = oxygen consumption in ml./min./$M.^2$ at standard temperature and pressure. Pyruvate and lactate values given in mg./100 ml. Hct. = hematocrit in per cent. Appearance time = time in seconds from injection of dye into antecubital vein until initial deflection of dye curve as recorded on densimeter. PVR = peripheral vascular resistance in dynes seconds cm.$^{-5}$

none of our patients was a high output state suspected on clinical grounds.

Part 1. Circulatory Studies in 7 Patients with Wernicke's Disease (table 1).

Cardiac Index and Peripheral Vascular Resistance Prior to Treatment. Cardiac index was measured in 7 subjects prior to treatment with thiamine. The mean value was 4.37 ± 2.11 L./min./$M.^2$, with a wide range of 1.4 to 6.5 L. Normal values in this laboratory in a series of 7 convalescent hospital patients were 3.53 ± 0.88 L./min./$M.^2$ The difference in this small series is not statistically significant. However, of the Wernicke's encephalopathy patients, 4 were above and 2 below the "normal" mean ±

1 standard deviation (fig. 1). All the patients with an elevated cardiac index exhibited a low calculated peripheral vascular resistance and, in general, both a resting tachycardia and an augmented stroke index (fig. 2). In these cases the resting pulse rate ranged from 102 to 115 per minute. However, in 2 of the 3 patients studied after treatment with thiamine there was a decline in stroke index associated with a fall in cardiac index; the third showed a slight rise in stroke index accompanied by a considerable drop in heart rate. Arteriovenous oxygen difference, as calculated from the Fick equation, was relatively low for all subjects who exhibited an increased cardiac index, indicating that the elevation of blood flow was not due to an increased oxygen requirement.

Immediate Response to Thiamine Administration (fig. 1). Two subjects received thiamine intravenously in a dose of 100 mg. immediately on completion of the control studies. In the first subject (JC), the control cardiac index of 5.7 L./min./M.^{2} fell to 4.8 L. 1 hour after thiamine, with minor changes in pulse rate and blood pressure. In the second (MS), the control value of 1.4 L./min./M.^{2} rose to 2.8 L. in 1 and 1½ hours, associated with increasing pulse rate and blood pressure, and progressive restlessness.

Response to More Prolonged Thiamine Administration (fig. 1). Six subjects were studied on a second occasion after they had received thiamine as the only vitamin supplement for 4 to 6 days. Of the 4 patients with elevated control cardiac indices (table 1, cases 1, 3, 4, and 6), all showed a decrease to the normal range with a corresponding rise in peripheral resistance. One patient (case 5) who originally had a normal cardiac index showed no change. Each of the remaining 2 patients (cases 2 and 7) with initially low values, remained low after treatment. Three patients were studied on a third occasion 7 to 36 days after the administration of a full diet and multiple vitamins. There was no further change except for a slight increase of cardiac index in 1 case.

Changes in Oxygen Consumption. Oxygen consumption was measured in 7 subjects before

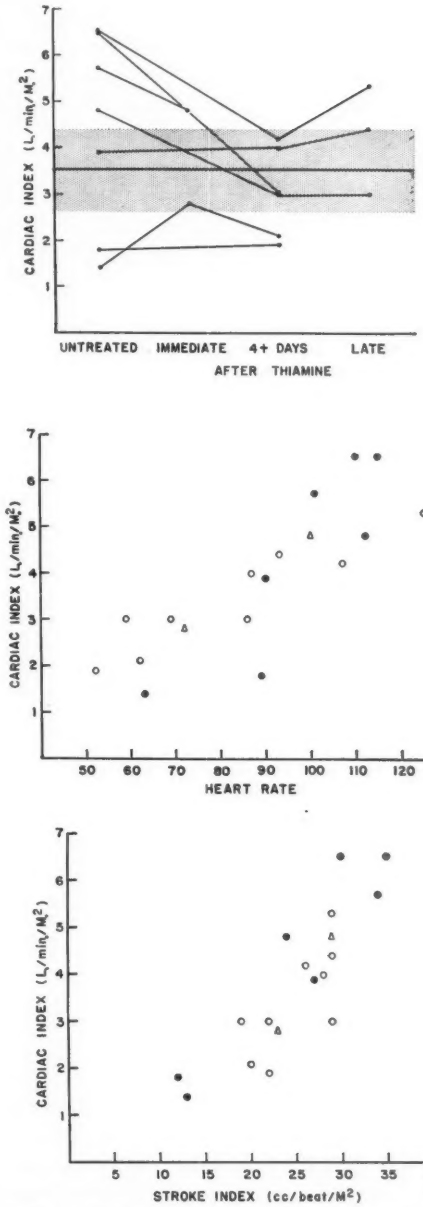


FIG. 1. *Top.* Cardiac index related to treatment in 7 patients. Shaded portion represents the "normal" mean cardiac index ± 1 standard deviation.

FIG. 2. Cardiac index related to heart rate (*middle*) and stroke index (*bottom*). ●—values prior to therapy; △—values 1–1½ hours after IV thiamine; ○—values after 4–36 days of therapy.

treatment with thiamine and in 6 subjects 4 or more days after treatment. Excluding a questionable figure of 215 in one (JK), pretreatment values averaged 149 ml./min./M.^{2} (range 128–167) and post-treatment values averaged 141 ml./min./M.^{2} (range 115–172). The apparent similarity of the pretreatment and post-treatment values for the entire group obscures the fact that of the 5 subjects with adequate determinations in both periods, 4 exhibited a decrease in oxygen consumption ranging from 16 to 22 ml., and the fifth an insignificant increase of 5 ml. Oxygen consumption correlated roughly with the cardiac index, but in the subjects having the highest pretreatment cardiac minute volume, the cardiac index was elevated out of proportion to oxygen consumption, as indicated by low values for calculated arteriovenous oxygen difference. Again, increase in blood flow was disproportionate to oxygen requirement.

Changes in Arterial Pressure and Pulse Rate. Mean arterial pressure averaged 88 mm. Hg before and 101 mm. Hg after treatment with thiamine in 7 subjects. Much of this minor rise in average pressure was due to an increase in mean pressure exhibited by 2 patients (EK and AN) who became hypertensive following specific therapy. The previous hospital record of AN disclosed hypertension of similar degree at intervals in the past.

Heart rate averaged 98/min. before and 80/min. after treatment with thiamine in 7 patients. This appears to be a significant decrease.

Changes in Blood Pyruvate and Lactate Levels. Elevation of fasting blood pyruvate to abnormal levels was found in all 6 patients in whom it was measured (table 1). A comparable increase in blood lactate was less consistently found. After administration of parenteral thiamine for 4 or more days, fasting pyruvate and lactate values declined to normal or nearly normal levels. Prior to therapy there was no obvious correlation between blood lactate or pyruvate values and cardiac index.

Part 2. Postural Responses in 12 Patients with Wernicke's Disease (table 2)

The cardiovascular response to tilting was grossly abnormal at some time during the study in 7 of the 12 patients tested. In 3 patients the blood pressure was completely unobtainable for varying periods of time during multiple tilts; in 2 of these (JK and AN) it was unobtainable throughout most of the 5 minutes of tilting on one occasion in each patient. It was of interest that despite such profound alterations in cardiovascular response, none of our patients complained of "dizziness" or "lightheadedness" during tilting, and syncope occurred on only one occasion during the entire study. However, postural "faintness" was a complaint in the histories of 3 of our more rational patients; 2 of these (EK and AN) demonstrated marked and prolonged postural hypotension on tilting.

In every case in which the blood pressure or pulse pressure fell abnormally there was ample evidence of reflex cardioacceleratory activity in terms of a rise in pulse rate of moderate to marked degree, but less consistent evidence of peripheral sympathetic activity (sweating, pallor).

Of the 6 patients studied before treatment, only 2 demonstrated an abnormality (MG and LH). Four patients were studied both before and after thiamine administration (EK, AN, LH, and WB). Of these, an abnormality was evident in only 1 patient (LH) before treatment. Two of these patients (EK and AN) showed inadequate compensation to tilting only *after* treatment with thiamine. Postural responses in these patients became markedly abnormal and remained so for relatively long periods following therapy. The fourth patient (WB) whose pressure readings were difficult to define on one occasion after treatment, exhibited at that time a response to tilting that was probably abnormal, in that his pulse pressure fell to about 20 per cent of control values. Marked and prolonged systolic "overshoot" of blood pressure occurred after return to the horizontal position in 2 subjects (MS and JK) on one occasion each.

The most marked abnormalities in this series were not restricted to the older nor to the most seriously incapacitated patients. EK and AN, aged 42 and 43, were 2 of the younger patients in the group. AN was in a relatively early phase of the disease and appeared well nourished.

TABLE 2.—*Postural Responses of Twelve Patients with Wernicke's Disease*

Patient, age, and sex	Days of treatment	Systolic pressure (mm. Hg)		Diastolic pressure (mm. Hg)		Pulse		Lowest pulse pressure (mm. Hg)	Duration of tilt (min.)	Normal or abnormal	Remarks
		Control	Max. change	Control	Max. change	Control	Max. change				
1. EK,42, M	0	130	+8	82	+6	108	+12	44	5	N	Marked dyspnea on slight exertion prior to therapy; history of postural "dizziness"
	6	145	−45*	100	−22	116	+36	22	5	Abn.	
	37	160	−90*	102	−42*	116	+24	12	5	Abn.	
	44	153	−43*	106	−18	104	+36	12	30	Abn.	
	44	158	−56*	93	−19	124	+16	22	30	Abn.	
2. AN,43, M	0	124	−8	89	+9	80	+36	16	5	N	History of postural "dizziness"; unobtainable B.P. readings throughout entire tilt on day 7; inconstantly unobtainable, day 10
	7	120	x	100	x	88	+44	x	5	Abn.	
	10	112	x	92	x	88	+40	x	10	Abn.	
	14	154	−16	115	+17	92	+28	10*	10	Abn.	
3. MS,57, M	5	117	−29	70	+10	64	+36	12	5	N	Marked post-tilt "systolic overshoot" day 5 (73 mm. Hg over control level); history of postural "dizziness"
	20	138	−36	75	+3	64	+20	24	5	N	
4. JK,65,M	6	104	x	69	x	76	x	x	5	Abn.	Unobtainable readings throughout entire tilt on one occasion, day 13; "systolic overshoot" (49 mm. Hg) on one occasion, day 6
	6	144	x	79	x	68	+20	x	5	Abn.	
	13	102	x	58	x	68	+24	x	5	Abn.	
	13	110	−60*	63	+23	73	+19	±10*	5	Abn.	
	13	88	x	50	x	72	+24	x	5	Abn.	
5. LH,68, M	0	105	x	73	x	96	+16	x	5	Abn.	B.P. readings unobtainable throughout entire tilt on one occasion, day 0
	0	111	−49*	76	x	88	x	x	15	Abn.	
	12	112	+10	61	+11	68	+20	36	20	N	
6. WB,52, M	0	134	−36	72	−20	104	+16	28	5	—	Pulse pressure fell to 20 per cent of control, day 5; syncope, day 0
	5	111	−15	64	+26	68	+24	±10	10	?N	
	29	132	+12	75	+15	84	+20	36	10	N	
7. ES,31,F	0	136	−14	93	+11	96	+28	26	5	N	
8. MG,63, F	0	100	−24	73	−11	98	+30	10*	5	Abn.	
9. FM,44, M	65	111	−13	79	+13	84	+36	12	5	N	
	75	110	+12	81	+19	84	+36	8*	5	Abn.	
10. JC,33,F	1	139	−12	84	+8	96	−4	40	5	N	
11. JE,45,M	6	102	−18	76	+12	60	+24	8*	5	Abn.	
12. TB,70,M	16	125	−11	63	+9	80	−4	42	5	N	

* Abnormal Change: Arbitrarily, a fall from the baseline of 40 mm. Hg systolic, 30 mm. Hg diastolic or a drop in pulse pressure to 10 mm. Hg or less was considered abnormal.

x = Reading unobtainable one or more times during tilt.

DISCUSSION

The main abnormalities found in this study were the alterations in cardiac output and the high incidence of postural hypotension. Tachycardia, elevated cardiac output, and low peripheral resistance were found in 4 of 7 patients. Of 6 patients subjected to cardiac output and postural studies, 3 showed both tachycardia and postural hypotension.

A number of factors might be implicated in the high output state encountered in our patients. Laennec's cirrhosis (and possibly "fatty liver") is known to be accompanied by an elevation of resting cardiac output in certain instances.[9] Of the 4 patients with an elevated cardiac output, 1 (JC) undoubtedly had cirrhosis and 3 were examples of "fatty liver." However, when the cardiac output is elevated in cirrhosis alone, it has not been shown to decline to normal levels in a few days, or in response to treatment with thiamine alone.

Two of the 4 patients with an elevated cardiac output were anemic, with hematocrit readings of 33 and 35 per cent. In 1 of these patients the cardiac output returned to normal 5 days after the original studies, but the he-

matocrit did not increase significantly. Moreover, an elevated cardiac output has not been found with anemia of this degree.[10]

A state of apprehension may elevate the cardiac output,[11, 12] but this factor seems unlikely in our patients, who were generally indifferent and apathetic. The possibility that an abnormal accumulation of blood pyruvate or lactate may affect the peripheral vascular system has been adequately excluded by other investigators; the intravenous administration of these substances and a large variety of other metabolites in both animals and man has not resulted in significant alterations of cardiovascular function.[13, 14]

A high cardiac output is characteristic of beriberi heart disease.[15-20] The high cardiac output seen in our patients may represent the same abnormality. Our cases showed no signs of congestive failure, but the cardiovascular manifestations of beriberi need not take this form alone. Keefer[21] studied 12 patients with neuritic beriberi who had no symptoms referable to the heart; yet 3 patients showed cardiomegaly and 10 had electrocardiographic abnormalities. It should be pointed out that electrocardiographic changes of the type seen in our patients have been reported in Wernicke's disease,[22] beriberi,[16] other types of nutritional deficiency,[23] experimental thiamine deficiency in man[24] and in animals,[25-31] all without congestive failure.

One can only speculate on the infrequent occurrence of congestive failure in our patients. In patients with neuritic beriberi the infrequency of congestive failure has been attributed to the paralysis and generally decreased physical activity that reduced the burden on the myocardium.[21, 32] Neuropathy was minimal in our patients, but the immobility necessitated by ataxia may have prevented the development of clinical myocardial insufficiency.

We can offer no satisfactory explanation for the low cardiac indices seen in 2 patients (MS and HC). Neither showed evidence of congestive failure. Both these patients were malnourished to the point of emaciation, a state that may be associated with slightly lowered cardiac output.[33] One patient (HC) was dehydrated and had arteriosclerotic heart disease; he died several days after his final study and postmortem examination disclosed an old apical myocardial infarction.

In attempting to explain the postural hypotension in our patients several pertinent factors should be considered. Undernutrition, present to some degree in all the patients, is commonly thought to be associated with poor vasomotor control. Postural hypotension, however, was not a prominent feature in a study on undernourished subjects.[34] The altered vasomotor response to tilting in the older age group[35] seems to be an inadequate explanation of the profound abnormalities found in the present series. Immobilization, however, in otherwise normal subjects, has been shown to predispose to orthostatic fainting in as short a period of time as 1 week.[36] It is possible that the immobilization imposed on our patients by ataxia may explain the high incidence of postural hypotension.

The concurrence of tachycardia, elevated cardiac output, low peripheral resistance, and postural hypotension can best be explained by a state of peripheral vasodilatation. One patient (EK) was known to have essential hypertension (increased peripheral resistance) before the onset of Wernicke's disease. During the acute phase of the illness his blood pressure became normal and peripheral vascular resistance was lowered. After treatment, he again became hypertensive with elevation of the peripheral vascular resistance. The presence, before treatment, of a low arteriovenous oxygen difference with an elevation of cardiac index disproportionate to the oxygen consumption also favors a state of peripheral vasodilatation.

It is interesting to speculate on the rapid reversal of tachycardia, elevated cardiac output, and low peripheral resistance following the administration of thiamine. This sequence of events suggests that a deficiency of this vitamin is in some way responsible for the production of these abnormalities. The fact that postural hypotension, or altered vascular response to tilting, appeared most commonly after specific therapy was instituted does not negate the role of thiamine deficiency in its production. Other cardiovascular symptoms such as cyanosis and electrocardiographic abnormalities may be-

come more prominent or may appear for the first time after the institution of specific therapy.[16] The cause of this phenomenon is unknown; possibly the increased metabolism accentuates the deficiency of other B vitamins or even of vitamin B_1.

Thiamine deficiency may have both a central and peripheral effect on the cardiovascular system. There is definitive evidence that the myocardium is affected in beriberi and in experimentally induced thiamine deficiency states;[16, 21, 24-31] more recent studies on myocardial metabolism in thiamine-deficient animals have demonstrated an abnormal utilization of pyruvate and lactate.[37, 38] From our observations it would also appear that acute thiamine deficiency, as manifested by Wernicke's encephalopathy, is accompanied by a state of peripheral vasodilatation, qualitatively similar to that found in beriberi.

Summary

Cardiovascular studies were performed on 7 patients with acute Wernicke's encephalopathy. Four of these showed a cardiac output elevated out of proportion to oxygen consumption and associated with low peripheral vascular resistance. These abnormalities reverted to normal after treatment with thiamine and bed rest. Resting tachycardia was a frequent occurrence. In 2 patients the cardiac output was low and remained low with treatment; in another it was normal.

Postural hypotension was found in 7 of 12 patients. The most profound abnormalities in the cardiovascular response to tilting occurred after treatment with thiamine.

It is suggested that these changes reflect an abnormal state of peripheral vasodilatation which, in turn, may be related specifically to thiamine deficiency.

Summario in Interlingua

Studios cardiovascular esseva executate in septe patientes con acute encephalopathia de Wernicke. In quatro de iste casos le rendimento cardiac esseva elevate foras de proportion con le consumption de oxygeno. Isto esseva associate con basse resistentia periphero-vascular. Tractamento con thiamina e allectamento resultava in le reversion del anormalitates mentionate. In duo patientes le rendimento cardiac esseva basse e remaneva basse post le tractamento. In un patiente le rendimento cardiac esseva normal.

Hypotension postural esseva constatate in septe ex 12 patientes. Le plus pronunciate anormalitates del responsa cardiovascular effectuate per inclination occurreva post tractamento con thiamina.

Es suggerite que iste alterationes reflecte un anormal stato de vasodilatation peripheric le qual, de su parte, es forsan relationate specificamente a carentia de thiamina.

Acknowledgment

The authors are grateful to the medical services of the Boston City Hospital for making the patients available for study, and to Drs. W. H. Abelmann, L. B. Ellis, and R. D. Adams for their generous help in preparing this paper.

References

[1] Phillips, G. B., Victor, M., Adams, R. D., and Davidson, C. S.: A study of the nutritional defect in Wernicke's syndrome. J. Clin. Invest. **31:** 859, 1952.

[2] Victor, M., Hope, J. M., and Adams, R. D.: A clinical study of Wernicke's disease. Tr. Am. Neurol. A., 1952, p. 178.

[3] McNeely, W. F., and Gravallese, M. A., Jr.: Measurement of cardiac output by dye dilution technique: use of an "integrated" sample collection in calibration of the photometric instrument. J. Appl. Physiol. **7:** 55, 1954.

[4] Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G.: Effect of exercise on circulatory dynamics of normal individuals. J. Appl. Physiol. **3:** 439, 1951.

[5] Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersey, M. I., and Richards, D. W.: Studies of the circulation in clinical shock. Surgery **13:** 964, 1943.

[6] Friedemann, T. E., and Haugen, G. E.: Pyruvic acid. II. The determination of keto acids in blood and urine. J. Biol. Chem. **147:** 415, 1943.

[7] Barker, S. B., and Summerson, W. G.: Colorimetric determination of lactic acid in biological material. J. Biol. Chem. **138:** 535, 1941.

[8] Seligson, D., and Shapiro, B.: Alpha-keto acids in blood and urine studied by paper chromatography. Analyt. Chem. **24:** 754, 1952.

[9] Kowalski, H. J., and Abelmann, W. H.: The

cardiac output at rest in Laennec's cirrhosis. J. Clin. Invest. **32:** 1025, 1953.

[10] Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, S. A., Jr.: The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J. Clin. Invest. **24:** 332, 1945.

[11] Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. J. Clin. Invest. **24:** 326, 1945.

[12] Hickam, J. B., Cargill, W. H., and Golden, A.: Cardiovascular reactions to emotional stimuli. Effect on the cardiac output, arteriovenous oxygen difference, arterial pressure, and peripheral resistance. J. Clin. Invest. **27:** 290, 1948.

[13] Haynes, F. W., and Weiss, S.: Responses of the normal heart and the heart in experimental vitamin B_1 deficiency to metabolites (pyruvic acid, lactic acid, methyl glyoxal, glyceraldehyde and adenylic acid) and to thiamin. Am. Heart J. **20:** 34, 1940.

[14] Wilkins, R. W., Weiss, S., and Taylor, F. H. L.: The effect and rate of removal of pyruvic acid administered to normal persons and to patients with and without "vitamin B deficiency." Ann. Int. Med. **12:** 938, 1938.

[15] Hayasaka, E., and Inawashiro, R.: Studies on the effect of muscular exercise in Beri-beri. Tohoku J. Exper. Med. **12:** 29, 1928.

[16] Weiss, S., and Wilkins, R. W.: The nature of cardiovascular disturbances in nutritional deficiency states (beri-beri). Ann. Int. Med. **11:** 104, 1937.

[17] Porter, R. R., and Downs, R. S.: Some physiological observations on the circulation during recovery from vitamin B_1 deficiency. Ann. Int. Med. **17:** 645, 1942.

[18] Burwell, C. S., and Dexter, L.: Beri-beri heart disease. Tr. A. Am. Physicians **60:** 59, 1947.

[19] Campbell, J. A., Selverstone, L. A., and Donovan D. L.: Studies on the high output cardiac failure of occidental beri-beri. J. Clin. Invest. **30:** 632, 1951.

[20] Lahey, W. J., Arst, D. B., Silver, M., Kleeman, C. R., and Kunkel, P.: Physiologic observations on a case of beriberi heart disease with a note on the acute effect of thiamine. Am. J. Med. **14:** 248, 1953.

[21] Keefer, C.: The beriberi heart. Arch. Int. Med. **45:** 1, 1930.

[22] Wallace, L., and Clarke, E.: Electrocardiographic changes in a case of Wernicke's syndrome. Ann. Int. Med. **31:** 675, 1949.

[23] Ellis, L. B.: Electrocardiographic abnormalities in severe malnutrition. Brit. Heart J. **8:** 53, 1946.

[24] Jolliffe, N., Goodhart, R., Gennis, J., and Cline, J. K.: The experimental production of vitamin B_1 deficiency in normal subjects. Am. J. M. Sc. **198:** 198, 1939.

[25] Zoll, P. M., and Weiss, S.: Electrocardiographic changes in rats deficient in vitamin B_1. Proc. Soc. Exper. Biol. & Med. **35:** 259, 1936.

[26] Swank, R. L., and Bessey, O. A.: Production and study of cardiac failure in thiamine-deficient pigeons. Arch. Int. Med. **70:** 763, 1942.

[27] Toman, J. E. P., Everett, G. M., Oster, R. H., and Smith, D. C.: Origin of cardiac disorders in thiamine-deficient cats. Proc. Soc. Exper. Biol. & Med. **58:** 65, 1945.

[28] Hundley, J. M., Ashburn, L. L., and Sebrell, W. H.: The electrocardiogram in chronic thiamine deficiency in rats. Am. J. Physiol. **144:** 404, 1945.

[29] King, W. D., and Sebrell, W. H.: Alterations in the cardiac conduction mechanism in experimental thiamine deficiency. Pub. Health Rep. **61:** 410, 1946.

[30] Hundley, J. M., and Sebrell, W. H.: Electrocardiographic alterations in adult rats as a result of acute thiamine deficiency. Pub. Health Rep. **61:** 847, 1946.

[31] Randles, F. S., Himwich, W. A., Homburger, E., and Himwich, H. E.: The influence of vitamin B_1 deficiency on the pyruvate exchange of the heart. Am. Heart J. **33:** 341, 1947.

[32] Wenkebach, K. F.: Heart and circulation in a tropical avitaminosis (beri-beri). Lancet **2:** 265, 1928.

[33] Howarth, S.: Cardiac output and the peripheral circulation in malnourished subjects. Abstracted, J. Physiol. **109:** 14, 1949.

[34] Taylor, H. L., Henschel, A., and Keys, A.: Cardiovascular response to posture and the problem of faintness and syncope in the semi-starved individual. Am. J. Physiol. **152:** 141, 1948.

[35] Morris, A. H., Shock, N. W., and Yiengst, M. J.: Age changes in heart rate and blood pressure responses to tilting and standardized exercise. Circulation **8:** 521, 1953.

[36] Deitrick, J. E., Whedon, O. G. D., and Shorr, E.: Effects of immobilization on various metabolic and physiologic functions of normal men. Am. J. Med. **4:** 3, 1948.

[37] Hackel, D., Goodale, W. T., and Kleinerman, J.: Effects of thiamine deficiency on myocardial metabolism in intact dogs. Am. Heart J. **46:** 883, 1953.

[38] Olson, R. E., Pearson, D. H., Miller, O. N., and Stare, F. J.: The effect of vitamin deficiencies upon the metabolism of cardiac muscle in vitro. J. Biol. Chem. **175:** 489, 1948.

Obliterative Brachiocephalic Arteritis

Pulseless Disease of Takayasu

By THOMAS B. GIBBONS, M.D., AND ROBERT L. KING, M.D.

Although a newcomer to American medical literature, this strange vascular disease of young adult women has been recognized abroad for many years. The etiology is obscure, but the pathologic findings are fairly well documented and the clinical picture is unusually consistent. An obliterative arteritis of the branches of the aortic arch results in severe ocular and cerebral damage. The disease process is relentlessly progressive and the prognosis for sight and life is poor. The present case was treated with corticosteroids and anticoagulants with apparent benefit. This disease should be considered when cataracts are encountered in young people and when arterial pressures and pulses in the upper extremities are absent.

THE ocular manifestations of a rare vascular disease afflicting branches of the aortic arch were first described in 1908 by Takayasu, a Japanese physician. The disease was not recognized in this country until 1952, when Caccamise and Whitman[1] reported a 19-year-old girl with characteristic clinical findings. However, 3 patients who may represent instances of obliterative brachiocephalic arteritis had been reported earlier under other diagnoses[2-4] and 3 probable cases have since been described.[5-7] In contrast, 68 cases are recorded in Japan,[6] and European authors have added 26 others.

DESCRIPTION

Confined almost exclusively to young adult women, obliterative brachiocephalic arteritis presents a remarkably well-defined clinical picture and a discouragingly progressive course leading to loss of visual and cerebral faculties and, ultimately, to blindness and death. The etiology is unknown. Ask-Upmark[8] has reviewed the cases occurring outside of Japan, Currier and associates,[6] have delineated the neurologic manifestations of pulseless diseases, and Caccamise and Okuda[9] have described the ocular findings. The differential diagnosis of this and other aortic arch syndromes has been well covered by Ross and McKusick.[5]

The basic fault is a loss of normal circulation to the head and upper extremities with symptoms and signs due to ischemia of the brain, eyes, head, and arms; hypersensitivity of the carotid sinus mechanism; and development of a collateral circulation.

The primary pathology is a chronic progressive arteritis involving all layers of the proximal segments of vessels arising from the aortic arch with eventual effacement of the lumen of the innominate, common carotid, and subclavian arteries. The iliac arteries can be involved and the ostia of the visceral branches of the aorta are occasionally included in the obliterative process. Classically, however, the arteritis is limited to the branches of the aortic arch. Microscopic examination of an affected artery discloses an inflammatory reaction involving all layers of the vessel wall reminiscent of the changes seen in smaller arteries with polyarteritis nodosa or temporal arteritis. The lumen of the artery is decreased in caliber or completely occluded. Thrombus formation contributes to the obliteration of the artery and attempts at recanalization may be seen.

A variety of etiologic agents has been considered, including syphilis and tuberculosis. However, Treponema have not been demonstrated in the lesions and the patients have invariably had negative serologic tests for syphilis. The occasional appearance of giant cells and granulomatous reaction in the vessel

From the Department of Medicine, the Mason Clinic, and the Virginia Mason Hospital, Seattle, Wash.

Presented at the Annual Meeting of the North Pacific Society of Internal Medicine, Victoria, B. C., October 1956.

wall has suggested tuberculosis but acid-fast organisms have not been recovered from or demonstrated in the diseased vascular tissue. Rheumatic or other types of preceding infectious processes have been noted in the anamnesis of many cases, particularly those reviewed by Ask-Upmark,[8] who pointed out that a large percentage of European cases are from countries bordering the North Sea, an area in which rheumatic infections are prevalent. The unusual frequency of this vascular disease in young women has led to interesting speculation but, unfortunately, has failed to illuminate the problem of etiology. Many believe that brachiocephalic arteritis is best considered a collagen disease.

Claudication occurs in the arms and jaw. Collateral circulatory routes develop largely from the intercostal arteries and supply the arms with sufficient blood to maintain nutrition of the tissues. As a result, gangrene of fingers does not occur. However, atrophy of nasal mucosa and perforation of the nasal septum have been described, as well as atrophy of the alveolar processes with loss of teeth. Focal areas of tissue necrosis may occur in the ears.

Early symptoms from the eyes have been termed "visual claudication" and consist of transient dimness of vision and diplopia. Pathologic alterations occurring in the eye secondary to ischemia include atrophy of the uveal tract, corneal opacities, cataract formation, and peripapillary looping of new vessels. A few instances of glaucoma have been observed.[10] Permanent visual impairment and blindness can result.

Cerebral symptoms also tend to be transient at first but distressingly recurrent with sensations of dizziness, paresis, or convulsions. The brain eventually becomes completely dependent upon the vertebral arteries for its supply of blood, and cerebral thrombosis is a common late development. Syncopal attacks can occur and have been attributed to a demonstrably hypersensitive carotid sinus mechanism, which may result from involvement of the sinus walls by the arteritis or from the lowered blood pressure in the carotid sinuses distal to the areas of arterial obliteration. Some patients with Takayasu's disease complain of tachycardia but other cardiac symptoms are seldom paramount although an occasional patient may progress to congestive heart failure on the basis of hypertension. In patients with iliac artery involvement, claudication has been present in the lower extremities as well.

Classically, arterial pulses and pressures are absent in the upper extremities but normal in the legs. Carotid artery pulsations may be absent or very faint and auscultation in the supraclavicular and carotid areas of the neck frequently discloses a continuous bruit with systolic accentuation. This vascular murmur probably arises in the diseased vessel itself as a result of a constant pressure gradient across the narrowed area.[7] Weak pulsations are at times palpable in the radial vessels, and an abnormally low arterial pressure with small pulse pressure may be detected in one or both arms. With involvement of the vessels to the legs, arterial pulses and pressures will be abnormal or absent in one or both lower extremities. Hypertension is occasionally recorded in the legs. Examination of the posterior thorax may disclose bruits or palpable dilated intercostal arteries serving as collateral channels.

Laboratory studies show few abnormalities. The erythrocyte sedimentation rate is generally accelerated. Serologic tests for syphilis are negative. Blood counts and chemical tests and the urine are normal. The electrocardiogram is normal in most cases. Electroencephalograms have seldom been described and are not specific. Fluoroscopic study gives no sign of the disease unless notching of the lower rib borders due to dilated intercostal vessels is observed. Angiocardiograms fail to demonstrate the proximal segments of the aortic branches although the more distal portion of these vessels may be visualized and appear normal.[11]

The present case demonstrates most of the characteristic symptoms and signs of the disease and is the first to be treated with corticosteroids and anticoagulants. The response to this therapy has been encouraging.

Case Report

Mrs. S. S., a 42-year-old white woman was admitted to the Virginia Mason Hospital in June 1956 for study of low blood pressure and pains in the left leg and right arm.* In 1951 she developed

* We are indebted to Dr. William V. King of Burlington, Washington, for referring this patient.

a deep aching in the region of the left shoulder and left side of the neck that lasted several days. Relief would be obtained only when the arm was placed completely at rest. Since 1951 she had 6 or 7 attacks of this nature involving the left shoulder, the left groin, and the right shoulder.

Fifteen months prior to entering the hospital, while walking on marshy ground wearing hip boots, the patient first noted cramping pains in the left calf relieved by rest. The right calf felt tired but was not painful. The left leg remained tender for 2 or 3 days after this walk and the slightest use caused pain. Since then, walking at a normal pace brought on claudication in the calf and, if she persisted, the claudication would spread into the left anterior thigh muscles. Resting gave relief and hurrying made it worse, as did walking up an incline.

For 9 months she had noticed that the left hand would become numb when carrying her lunch pail. The more shirts and jackets worn, the faster the hand would go numb. This symptom persisted and 4 months prior to hospitalization she first developed cerebral and ocular symptoms, which occurred in attacks coming on as frequently as twice a day or as infrequently as twice each week. The initial symptom of these attacks was a feeling of weakness in the eyes "as if they would cross." Then a sensation of slow gyrations in the head and partial loss of balance would develop. If she tried to walk during these spells, she weaved. Lying down shortened their duration. Each spell lasted from 4 to 10 minutes and was followed by nausea. One month after the appearance of these symptoms her blood pressure was found to be low, at 70/60 mm. Hg in the arm.

Within a month of coming here she first noticed claudication in the right arm involving the deltoid and biceps muscles that was brought on by repetitive motions of the arm such as raking the lawn or painting walls. About the same time jaw claudication first appeared with aching in the masseter muscles and in the neck when chewing meat or other fibrous foods. This aching discomfort in the jaw and neck would stop when she ceased chewing.

Past History. The patient was born in 1914 in Canada. At age 5 she fell and fractured the right clavicle but there was no other history of injury. She had the usual childhood diseases without complication. The menarche was at age 12 and menses were regular. At age 29 both Fallopian tubes and one ovary were removed, apparently because of cysts and dysmenorrhea. She had never been pregnant. There was no history of venereal infection. The teeth were replaced many years ago by dentures. For 3 years she had been treated elsewhere for a mild glaucoma. She smoked 1 package of cigarettes each day. Review of systems was negative.

Family History. The patient is the eighth of 10 children. Her father, of English descent, is 80 years old, active, and well. Her mother, of French and German extraction, died at age 76 after a fractured hip; she was a mild diabetic for the last 5 years of her life. No member of the patient's family has been afflicted with an illness similar to hers.

Physical Examination. She was a normally developed, adequately nourished woman, 5′3″ tall, weighing 135 pounds, and edentulous. The nasal mucous membranes were atrophic but there was no perforation of the septum. The ears were normal. Ophthalmoscopic examination disclosed slight glaucomatous cupping but no evidence of cataracts, corneal opacities, or vascular looping in the region of the optic disks. Carotid pulsations were barely perceptible, and in the left carotid triangle of the neck a continuous bruit was clearly audible. There was systolic accentuation of the murmur but it persisted throughout diastole. Neither axillary artery was pulsatile to palpation. A very weak right brachial artery pulsation was present. Both radial arteries were weakly palpable at times but ulnar pulses were absent. The lungs were normal to examination and the heart was not enlarged on percussion. There were no palpable thrills or audible cardiac murmurs, and the heart tones were regular and of good quality without accentuation or muffling. The liver, spleen, and kidneys were not enlarged, nor was there any abdominal mass, fluid, or localized tenderness. The abdominal aorta was normally pulsatile, and pulsations were strong in the right femoral artery but weak in the left. Auscultation disclosed a systolic bruit over the left femoral vessel. The right popliteal and dorsalis pedis pulses were normal but the left popliteal and dorsalis pedis arteries and both posterior tibial vessels were nonpulsatile. Pelvic and rectal examinations were negative and the deep tendon reflexes and sensory perception were normal. There was no pain or tenderness on palpation of any of the muscle groups or with movement of any of the joints, all of which had a free and normal range of motion.

Blood pressure was determined with great difficulty in the arms. With the patient supine the systolic pressure in both arms was around 75 to 80 mm. Hg, both on palpation and auscultation. By auscultation, diastolic pressure was estimated to be around 70 mm. Hg. With the patient sitting up or standing, an arterial pressure could not be detected in either arm. At times a satisfactory reading was unobtainable in any position. Blood pressure in the legs, obtained with a 14-cm. cuff on the lower thigh, was 145/80 mm. Hg on the right and 90/80 mm. Hg on the left. By palpation with the cuff on the calf the systolic blood pressure in the right dorsalis pedis artery was measured at 120 mm. Hg. An intra-arterial blood pressure of 120/80 mm. Hg was recorded from the right femoral artery. Intra-arterial pressures were not taken in any of the involved extremities because of the small risk of further compromising the circulation to these parts.

Laboratory studies were all normal and included hemoglobin, total and differential leukocyte counts,

sedimentation rate, serologic test for syphilis, urinalysis, blood cholesterol and calcium, serum sodium and chloride, postcibal blood sugar, and a Robinson-Kepler-Power test. The electrocardiogram was normal. A chest film disclosed a heart shadow normal in size and contour, clear lung fields, and no rib notching. Fluoroscopy showed no evidence of aneurysm or other abnormality of the aorta or heart. A film of the abdomen was negative for calcification in the adrenal glands or vessels. Venous pressure in the right antecubital vein was 118 mm. of water, with the reference level 10 cm. from the back. Circulation time arm-to-tongue employing Decholin was 11 seconds. An electroencephalogram, 8-electrode bipolar localizing type, disclosed nondescript changes of low voltage, rapid variety type from all areas. A rare 10 to 12 per second alpha wave appeared in the posterior derivations. No high voltage slow activity was noted at any time during the recording and no paroxysmal dysrhythmias. There were no focal artifacts. The tracing was classified abnormally rapid, not specifically diagnostic.

Hospital Course. The patient remained afebrile and ambulatory. Prednisone, 10 mg. was administered orally every 6 hours. Dicumarol was employed to maintain the prothrombin concentration between 10 and 20 per cent of the control. The patient was discharged after 10 days to continue the same medications.

Results of Treatment. After 6 weeks of therapy the patient returned for reevaluation. There were signs of mild steroid effect with early mooning of the face. She reported a gradual subjective improvement, having been free of jaw and arm claudication since leaving the hospital and she also noted an increased capacity for walking before the appearance of claudication in the left calf. She had not been bothered with further cerebral symptoms but continued to have occasional transient blurring of vision and sensation as though the eyes were about to cross. Pulsations seemed stronger in the common carotids and the left femoral vessel. The radial pulses were still very weak and the ulnar pulsations remained absent. The left dorsalis pedis pulse was at times thought to be present; however, blood pressure determinations in arms and legs were not appreciably altered.

At this juncture further studies were carried out which, unfortunately, had not been done before treatment was begun. The platelet count was 180,000 and 200,000 on 2 occasions. An angiocardiogram was performed with 40 ml. of 70 per cent Neo-Iopax. The first portion of the innominate artery, the entire left subclavian artery, and the proximal segment of the left common carotid artery were not visualized. The right subclavian artery could be faintly traced at its junction with the right common carotid but not distal to this point. However, the axillary arteries and the distal portions of the carotid arteries, including their bifurcations, were clearly seen and appeared normal. The failure of the dye to outline the proximal segments of the branches of the aortic arch was considered in keeping with the presumed presence of arteritis in these vessels with narrowing of the lumen. The arch itself was well opacified in several of the exposures and appeared entirely normal without evidence of aneurysm or congenital malformation. Visualization of the more distal segments of the carotid vessels and of the axillary arteries showed that none of the involved arteries had been completely occluded. Collateral vessels were not seen.

Discussion

A positive diagnosis of obliterative brachiocephalic arteritis on clinical grounds alone is not possible at this time. Ross and McKusick's[5] comprehensive discussion of the various entities that may present as the aortic arch syndrome emphasizes the difficulties of the differential diagnosis. Given a young woman without evidence of aneurysm, congenital anomaly, or trauma, the likelihood of Takayasu's disease is very good.

The symptoms and signs of the aortic arch syndrome presented by our patient prior to the institution of steroid and anticoagulant therapy would be difficult to explain on any basis other than an obliterative brachiocephalic arteritis. Except for the fractured clavicle in childhood there was no history of trauma and no evidence of aortic aneurysm or dissection or syphilitic infection. The aortic arch appeared entirely normal on angiocardiography. The presence of degenerative atherosclerosis with thrombotic occlusion of the innominate, carotid, and left iliac vessels remains a possibility but would seem unlikely in a woman of her age free of diabetes, hypertension, or evidence of deranged lipid metabolism or arteriosclerosis elsewhere. This patient did vary from the typical case of brachiocephalic arteritis in 3 respects: there was no objective evidence of organic damage to the eyes beyond glaucoma, she did not have carotid sinus syncopal attacks, and she apparently did have involvement of the left iliac artery. However, all these variations have been described in patients with Takayasu's disease.

The prognosis of patients with obliterative brachiocephalic arteritis is poor. The duration of symptoms in reported cases ranged from 6

months to 14 years. The average time from onset of symptoms to the time of reporting or to death was 5.1 years for the 26 cases reviewed by Ask-Upmark.[8] Blindness and cerebral thrombosis are the greatest threats to the patient with pulseless disease.

A variety of therapeutic measures have been attempted but no one has reported favorable results except for apparent improvement in 1 probable case treated with penicillin.[6] Cortisone or allied steroids have not been employed except briefly in 1 of Ask-Upmark's patients.[8] Because that patient's cataracts appeared to worsen, the drug was discontinued after only 1 week of therapy. We decided to try prednisone in the present case in an attempt to control, or even reverse, a presumed inflammatory arteritis. We were pleased to note improvement of the patient's symptoms. Although the response to this therapy was judged on subjective grounds, the patient was confident that her exercise tolerance for walking was increased and insisted that her cerebral symptoms had cleared as had jaw and arm claudication. Even considering the known euphoria and sense of well being often associated with use of these steroids, we believe that an actual improvement may well have taken place. As previously described, some of the arterial pulses seemed stronger to the examiners although blood pressure levels had not changed appreciably.

At the present time the patient is being maintained on 15 mg. of prednisone per day and sufficient Dicumarol to provide a desired degree of hypoprothrombinemia. We intend to reevaluate the patient's status at frequent intervals, watching particularly for the appearance of organic changes in the eyes. If visual or cerebral symptoms become worse, arteriography will be repeated and the feasibility of vascular grafting or prosthetic replacement of the diseased vessel segments appraised.

Summary

An apparent instance of a rare vascular disease, obliterative brachiocephalic arteritis, occurring in a 42-year-old woman is described. Prednisone and Dicumarol were employed therapeutically with encouraging results. Although the present case is but the third example of this disease to be reported in this country, 5 probable cases have been described under other diagnoses. In contrast, nearly 100 cases have been recognized elsewhere in the world, chiefly in Japan and Europe.

Summario in Interlingua

Es describite un caso apparente del rar morbo vascular, arteritis brachiocephalic obliterative. Le patiente esseva un femina de 42 annos de etate. Prednisona e Dicumarol esseva usate con incoragiante resultatos therapeutic. Ben que le presente caso representa solmente le tertie exemplo de iste morbo reportate in le Statos Unite, 5 casos probabile esseva describite sub altere diagnoses. Per contrasto con isto, quasi 100 casos ha essite recognoscite in altere partes del mundo, principalmente in Japon e Europa.

REFERENCES

[1] Caccamise, W. C., and Whitman, J. F.: Pulseless disease: A preliminary case report. Am. Heart J. **44:** 629, 1952.

[2] Elliot, A. H., Usher, N. T., and Stone, C. S.: Bilateral carotid sinus denervation in a patient having syncopal attacks and a congenital vascular anomaly. Am. Heart J. **17:** 69, 1939.

[3] Giffin, H. M.: Reversed coarctation and vasomotor gradient: Report of a cardiovascular anomaly with symptoms of brain tumor. Proc. Staff Meet., Mayo Clin. **14:** 561, 1939.

[4] Aggeler, P. M., Lucia, S. P., and Thompson, J. H.: A syndrome due to occlusion of all arteries arising from the aortic arch. Am. Heart J. **22:** 825, 1941.

[5] Ross, R. S., and McKusick, V. A.: Aortic arch syndromes; diminished or absent pulses in arteries arising from arch of aorta. Arch. Int. Med. **92:** 701, 1953.

[6] Currier, R. D., De Jong, R. N., and Bole, G. G.: Pulseless disease: Central nervous system manifestations. Neurology **4:** 818, 1954.

[7] Myers, J. D., Murdaugh, H. V., McIntosh, H. D., and Blaisdell, R. K.: Observations on continuous murmurs over partially obstructed arteries. Arch. Int. Med. **97:** 726, 1956.

[8] Ask-Upmark, E.: On the "Pulseless Disease" outside of Japan. Acta med. scandinav. **149:** 161, 1954.

[9] Caccamise, W. C., and Okuda, K.: Takayasu's or pulseless disease. Am. J. Ophth. **37:** 784, 1954.

[10] Hsioh-Teh, C., An, C., and Fu-Hsi, C.: The pulseless disease. Chinese M. J. **73:** 163, 1955.

[11] Shimizu, K., and Sano, K.: Pulseless disease. J. Neuropath. & Clin. Neurol. **1:** 37, 1951.

The Ausculatory Gap in Arteriosclerotic Heart Disease

By Simon Rodbard, M.D., and Jack Margolis, M.D.

Auscultatory gaps, found in some patients with arteriosclerotic heart disease, can be elicited in others by reducing blood flow in the extremity. Reactive hyperemia eliminates the gap in every instance. The gap therefore appears to represent a vasospastic disturbance that limits the blood flow to the extremities, despite the presence of an enhanced pressure head.

THE auscultatory gap, recorded commonly in patients with systolic hypertension or with aortic stenosis, probably represents an undefined disturbance in cardiovascular function. Aside from this, the gap may have practical importance, since significant errors in the estimation of the blood pressure may result when its presence is not recognized.[1-5] The present study of the gap extends previous investigations into mechanisms of sound production at the brachial artery during the indirect measurement of the blood pressure.[6-10] Technics for enhancing or eliminating the gap, and an analysis of its physiologic mechanisms and clinical significance are presented.

Methods

Twenty ambulatory male patients, 65 to 78 years of age, with systolic blood pressures of 170 mm. Hg or higher, were selected for study. The clinical diagnosis of arteriosclerotic heart disease was based on physical examination and electrocardiographic and roentgenologic study.

At least 10 blood pressure determinations were made on each patient. In some of these, a dynamic microphone placed in the antecubital fossa transmitted the arterial sounds to a Sanborn twin-beam instrument, which recorded them simultaneously with lead II of the electrocardiogram. Blood pressure determinations were made as the cuff pressure was deflated at about 3 mm. Hg per second.

From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y., and the Medical Service, Veterans Administration Hospital, Big Spring, Tex.

Introductory phases of this study were begun at the Cardiovascular Department (Dr. L. N. Katz, Director), Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

The Chronic Disease Research Institute is supported by grants-in-aid from the New York State Department of Health and other public and private sponsors.

Aided by grant H-2271 from the National Heart Institute.

Results

Of the twenty patients selected for the study only 3 had a gap while recumbent (table 1). In the sitting position, 2 of these continued to have a gap and 4 other patients also showed gaps. In the standing position, gaps were found in 7 of the subjects, but not always the ones who showed gaps in the recumbent or sitting positions. Eleven of the patients had a gap at least once during the testing periods. While there was no consistent effect of body position, the increased likelihood of gap in the sitting or standing position was apparent.

The gaps began 10 to 50 mm. Hg below the systolic pressure and had spans as large as 30 mm. Hg. In general, patients with higher systolic blood pressures had a greater tendency to have a gap.

Comparison of Auscultation and Phonocardiography. In some patients, gaps noted on direct auscultation of the arterial sounds were shown to be due to the subaudible amplitude of vibrations in the gap zone, which electronic amplification made clearly audible. Phonocardiographic records showed the vibrations in the gap range to have a markedly lower amplitude than the sounds in the other pressure ranges (fig. 1). These results indicated that the gap was due in part to a limitation in hearing, rather than to a complete absence of vibrations. This concept was supported by studies in which an induced reactive hyperemia enhanced the intensities of all the arterial sounds.

Elimination of the Gap. The gap was eliminated in every instance by producing a local reactive hyperemia. This was accomplished by increasing the cuff pressure to a level above systolic and then having the patient clench the fist 25 times; the increased blood flow following release of the tourniquet brought all the ar

TABLE 1.—*Auscultatory Gap in Twenty Patients*

Case	Age	Diagnosis	Blood Pressure (mm. Hg)	Ranges of the auscultatory gap (mm. Hg)						
				Lying	Sitting	Standing	With tourniquet			After local exercise
							Lying	Sitting	Standing	
		Generalized arteriosclerosis plus:								
1	68	—	180/90	0	0	0	0	0	0	0
2	72	—	170/90	0	0	0	0	0	0	0
3	76	—	195/65	0	0	0	0	0	0	0
4	66	Chronic bronchitis	210/100	0	0	0	190–170	190–170	180–160	0
5	66	Osteoarthritis	190/100	0	0	0	160–150	160–150	170–160	0
6	66	Meningovascular syphilis	190/90	0	0	0	0	0	160–130	0
7	73	Meningovascular syphilis	180/90	0	0	0	160–130	160–140	160–140	0
8	76	—	175/65	0	0	0	150–140	140–120	140–120	0
9	77	Meningovascular syphilis	180/70	0	0	0	0	160–140	160–140	0
10	65	—	240/70	0	210–180	0	0	210–170	200–180	0
11	66	Chronic glomerulonephritis	250/110	0	0	210–200	230–200	220–200	230–200 170–160	0
12	68	Osteoarthritis	260/110	0	0	210–180	200–190	200–180	230–210	0
13	70	Chronic glomerulonephritis	230/110	0	0	210–190	0	210–180	210–180	0
14	70	Carcinoma of lung	190/60	0	170–140	0	170–140	160–120	0	0
15	71	Carcinoma of lung	230/90	0	200–170	0	200–180	210–200	0	0
16	71	Osteoarthritis	175/60	0	0	150–140	160–140	160–145	160–140	0
17	78	—	180/90	0	140–120	0	160–140	160–140	160–140	0
18	78	—	220/90	195–170	0	190–170	200–180	0	190–170	0
19	65	—	210/90	190–170	200–180	200–180	190–160	190–160	190–170 160–140	0
20	65	—	290/110	240–220	240–220	260–240 210–200	240–220	240–220	250–220	0

terial sounds above the hearing threshold. Such localized exercise has been shown by plethysmographic[11] and other technics to produce a marked increase in blood flow. This effect was enhanced when the blood flow to the extremity was restricted by tourniquet during the exercise period. Coincident with the increased blood flow, all the arterial sounds were markedly increased in intensity and duration, and a gap was no longer present.

It has been shown in previous studies that reactive hyperemia, enhancing the blood flow to the region, increases the intensity and duration of the arterial sounds.[9] The maneuver has no significant effects on the central blood pressure or on the pulse wave.

The results suggested, therefore, that the occurrence of the gap was associated with a reduced blood flow to the extremity. This concept was tested by the application of a tourniquet to the forearm for the purpose of reducing the blood flow to the arm.

Induced Auscultatory Gaps. To diminish the blood flow to the arm, a tourniquet, consisting of a sphygmomanometer cuff inflated to a pressure of 250 mm. Hg, was applied to the forearm. The blood pressure was then recorded according to conventional technics by increasing the pressure in the cuff on the upper arm to a level above systolic and permitting the cuff pressure to fall slowly.

Under these conditions all the arterial

sounds were markedly decreased in intensity and duration, and the likelihood of a gap was increased. A gap was now found in all but 3 of the 20 subjects. The effect of position was inconsistent in the occurrence of these gaps. Similar tourniquet studies carried out on 20 individuals without evidence of cardiovascular disease produced gaps in none of the subjects tested.

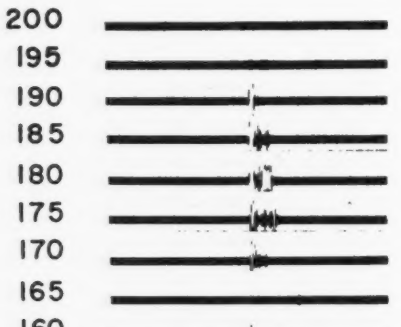


FIG. 1. Arterial sounds demonstrating the auscultatory gap. The figure comprises a set of arterial sounds obtained as the cuff pressure was lowered from above systolic to below diastolic levels in a single continuous recording in a patient. Deviations from the horizontal galvanometer trace represent sound vibrations. The arterial sounds at systolic pressure (190 mm. Hg) are seen to have a greater intensity than those in the gap range (165 mm. Hg) where they virtually disappear. The amplitude and duration of the vibrations then increase again as the cuff pressure falls until the diastolic pressure is reached (105 mm. Hg) at which time no further audible vibrations are noted.

These results, showing the increased tendency to gap in patients with arteriosclerotic heart disease during maneuvers that reduce blood flow to the extremity, indicate that the volume of blood flowing into the extremity is an important mechanism in the genesis of the gap. Since the systolic and mean blood pressures are high in such patients with arteriosclerosis, a vasoconstrictive tendency in the blood vessels of the extremity would appear to be suggested.

DISCUSSION

Our findings of spontaneous gaps in 3 of the 20 subjects examined suggest that this phenomenon is not uncommon in the aged patient with arteriosclerotic heart disease and systolic hypertension. The likelihood of a gap being present was increased in patients when the systolic blood pressure was excessively elevated, i.e., above 220 mm. Hg. It was found less commonly when the patient was recumbent than when he was sitting or standing. A double gap was elicited on 3 occasions.

The intensities and durations of the arterial sounds heard during blood pressure measurement are dependent, in part, on the relation of cuff pressure to blood pressure. These sounds are conventionally divided into 5 phases, but actually the pattern of the sounds may vary significantly from individual to individual, as well as changing with various cardiovascular conditions. The systolic level is usually characterized during the decompression of the cuff by a tapping sound (first phase) that increases in intensity and then sometimes changes to a softer sound (second phase). As the cuff is further deflated, an added murmur-like rumble increases the duration of the sound, ushering in the third phase. When the cuff pressure approaches the diastolic level, the sounds become muffled (fourth phase) and finally can no longer be heard (fifth phase).

The auscultatory gap in arteriosclerotic heart disease is most frequently noted within 40 mm. Hg of the systolic pressure when the arterial sounds become softer, during the second phase.

The present data are consonant with the point of view that the occurrence of the gap is

related to a reduction in the intensities of the vibrations in the gap range, rather than to their complete elimination. That vibrations are actually produced in the gap range is suggested by the consistent demonstration of sounds in this range with adequate electronic amplification. The amplitudes and durations of the sounds in the gap range, however, are significantly less than those recorded in other ranges of the blood pressure determination.

The magnitude and duration of the vibrations produced at the compressed artery are affected to a marked degree by the blood flow through the vessel, as indicated by both clinical and hydrodynamic studies. With increased flow the intensities and durations of the sounds are increased. This effect is seen strikingly after the induction of reactive hyperemia, which intensifies all the arterial sounds so that a gap can no longer be demonstrated.

By contrast, when the blood flow through the compressed artery is obstructed as by a tourniquet immediately beyond the stethoscope, the arterial sounds become much weaker and more difficult to hear. The likelihood of a gap is thereby enhanced. After placement of the tourniquet a gap could be elicited in patients in whom none was discerned during the previous blood pressure measurements.

The pulse is present at the radial artery during the gap phase even though the sounds at the brachial artery fade. The pulsations may be very forceful even though only a limited blood flow is taking place through the palpated artery.[8] Thus, the strength of the pulse, often used as an index of extremity blood flow, may be marked, despite evidence that the blood flow is restricted.

The present findings indicate that the arterial sounds have value in the appraisal of the clinical status of the patient. Thus, when the sounds are faint, a reduced blood flow to the extremity may be presumed. This reduced peripheral flow might be expected in older patients with systolic hypertension and arteriosclerotic heart disease in whom cardiac reserve and output are limited. It is likely that active vasoregulatory mechanisms[12] ration the major portion of the restricted cardiac output to vascular beds in the central nervous system, the heart and other vital structures, while the extremities receive only a limited flow. This effect is probably enhanced in the sitting or standing position. Clinical evidence of a reduced blood flow to the arms and legs in arteriosclerotic heart disease is seen in the cold extremities, intermittent claudication, and peripheral cyanosis so common in this age period. The presence of diminished arterial sounds and especially of a gap may thus be considered as a sign of peripheral vasospastic activity.

Summary

Evidence is presented that auscultatory gaps heard in patients with arteriosclerotic heart disease may be associated with a reduced blood flow to the extremity. Further reduction of such flow, as by application of a tourniquet, increased the likelihood of a gap. Contrariwise, increase in extremity blood flow eliminated the gap in every instance. Vibrations are present in the gap range, but these are subaudible; electronic amplification may bring these sounds to audible levels. The clinical implications of these findings are discussed.

Summario in Interlingua

Es documentate le these que le lacunas auscultatori notate in patientes con arteriosclerotic morbo cardiac es associate con un reduction del fluxo sanguinee verso le extremitates. Reductiones additional de ille fluxo—per exemplo per le application de un tourniquet—augmenta le probabilitate del occurrentia de lacunas. Del altere latere, le augmento del fluxo sanguinee verso le extremitates eliminava le lacunas in omne casos. Il existe vibrationes durante le lacunas, sed iste vibrationes es infra le limines del audibilitate. Per medio de un amplification electronic il es possibile render tal sonos audibile. Es discutite le implicationes clinic de iste constatationes.

REFERENCES

[1] Cook, J. E., and Taussig, A. E.: Auscultatory blood pressure determination: A source of possible error. J.A.M.A. **68:** 1088, 1917.

[2] Mudd, S. G., and White, P. D.: The auscultatory

gap in sphygmomanometry. Arch. Int. Med. **41:** 249, 1928.

[3] GLADSTONE, S. A.: Concerning the mechanism of production of the Korotkoff sounds and their significance in blood pressure determinations. Bull. Johns Hopkins Hosp. **44:** 122, 1929.

[4] BRIM, C. J., AND WOLFFE, J. B.: The silent or auscultatory gap. M. Rec. **139:** 113, 1934.

[5] BERRY, M. R.: The mechanism and prevention of impairment of auscultatory sounds during determination of blood pressures of standing patients. Proc. Staff Meet., Mayo Clin. **115:** 699, 1940.

[6] RODBARD, S., AND SAIKI, H.: Flow through collapsible tubes. Am. Heart J. **46:** 715, 1953.

[7] —: Flow through collapsible tubes: Augmented flow produced by resistance at the outlet. Circulation **11:** 280, 1955.

[8] —, AND JANNOTTA, F.: An analysis of oscillometric pulsations. Circulation **7:** 922, 1953.

[9] —: The significance of the intermediate Korotkoff sounds. Circulation **8:** 600, 1953.

[10] —, RUBINSTEIN, H. M., AND ROSENBLUM, S.: Arrival times and calibrated pulse wave contours determined indirectly by arterial sound recordings. Am. Heart J. In press.

[11] ABRAMSON, D. I.: Vascular Responses in the Extremities of Man in Health and Disease. Chicago, University of Chicago Press, 1944.

[12] RODBARD, S., AND KATZ, L. N.: The neurogenic control of the blood vessels. Circulation **12:** 445, 1955.

Rifkin, H.: The Kimmelstiel-Wilson Syndrome: Clinical Aspects. J. Mt. Sinai Hosp. **23:** 674 (Sept.-Oct.), 1956.

Although there is little doubt that a clinical syndrome characterized by diabetes, edema, hypertension, proteinuria, azotemia, and diabetic retinopathy is found in about 10 to 15 per cent of patients with the specific Kimmelstiel-Wilson nodular lesion of the glomerulus, similar symptoms and signs may be found in patients without this specific lesion. The diagnosis of this syndrome is further helped by the finding of doubly refractile lipoid cells and casts in the urinary sediment and may be confirmed during life by renal biopsy. It is also well known that anatomically proved cases of this condition may not be identified during life because of the paucity or lack of clinical findings. The earliest clinical signs of the disease may be detected in diabetic patients by repeated ophthalmoscopic examinations for the retinal micro-aneurysms that coexist with the glomerular involvement. Doubly refractile bodies in the urine may also possibly be an early finding.

In regard to pathogenesis, controversy exists as to the effects of control of diabetes on the development of the renal and retinal lesions. In the author's experience no real differences in the insulin requirements or frequency of episodes of acidosis are apparent between diabetic patients with and without the specific renal lesion. It has been established that the duration of diabetes is an important factor in pathogenesis, but the time factor may vary from as little as 6 years to as long as 25 years. Some interesting biochemical alterations regarding tissue concentrations of mucopolysaccharides, lipids, and lipoproteins have been reported in this condition, but the present evidence is too fragmentary to allow a definite causal relationship of these substances to the renal and glomerular lesions. Recent studies have also indicated a possible relationship between increased pituitary-adrenal cortical activity and the development of the specific vascular lesions, but it is much too early to come to any definite conclusions. As yet no real therapeutic regimen is available for these patients.

SAGALL

Comparison of Mercurial Diuretics and Bed Rest in Normal and Toxemic Pregnancies

By N. S. Assali, M.D., J. Voskian, M.D., and J. Roller, M.D.

With the technical assistance of M. Ross

Recent reports have indicated that oral organomercurial compounds are effective in promoting diuresis in edematous states. In the majority of these studies, however, salt restriction, bed rest, and other medications were used. Therefore, the diuretic effects of the oral mercurials alone have not been properly assessed. In the present report, the effects of oral mercurials on water and electrolyte excretion were studied in normal and toxemic pregnancies and were compared to effects induced by bed rest and by injectable organomercurial agents.

THE effectiveness of mercurial diuretics when given parenterally has been well demonstrated in man and animals.[1] Recently oral organomercurial preparations have been used by several authors in the management of edematous states.[2-6] Satisfactory results have been reported depending to a large extent on the dose given. In most of these reports, however, low-sodium diet, other diuretic and cardiac medication, or bed rest was also used. Therefore, the efficacy of the orally administered mercurials alone has not been satisfactorily assessed.

The present study was aimed at investigating the action of oral organomercurial agents on the renal excretion of water and electrolytes in the edema of normally pregnant and toxemic patients. The effects of bed rest alone were similarly investigated. These results were then compared to those obtained from a similar group of patients to whom intramuscular organomercurial drugs had been administered.

Material and Methods

A total of 37* patients whose ages varied from 18 to 40 years were studied: 29 had toxemia of pregnancy and 8 were normally pregnant. All patients were in the last trimester of gestation. The criteria for the diagnosis of toxemia have been outlined elsewhere.[7]

The patients were in the hospital at bed rest without any specific medication throughout the periods of study (the normally pregnant patients were permitted to ambulate for 1 to 2 hours a day). They all received the same daily diet, that contained approximately 100 Gm. of fat, 100 Gm. of protein, 200 Gm. of carbohydrate, and 85 mEq. of sodium as sodium chloride.

The study was divided into 3 consecutive periods. The first period lasted from 4 to 5 days and served as a control. During the second period, which lasted from 4 to 5 days, an organomercurial compound was given either orally in 3 doses totaling 6 to 8 tablets or intramuscularly in the dose of 1 to 2 ml. every 24 hours. The third period served as a recovery period and lasted for 3 to 4 days. In assessing the effects of bed rest alone, a group of 4 patients at bed rest without other therapy were studied during the same number of days.

Two oral and 2 injectable organomercurial compounds were used. Neohydrin† (3-chloromercuri, 2-methoxypropyl urea) was given orally to 5 normal and 10 toxemic patients and Metrox† (1-(3-hydroxymercuri-2-methoxypropyl)-biuret) was given to 3 normal and 5 toxemic patients. Mercuhydrin (mellarulide) and Mersoben,‡ 3-[2-hydroxy-3 (-d-glucopentahydroxyhexyl-mercapto mercuri) - propyl]-d-mannitol were given intramuscularly to 5 toxemic patients each.

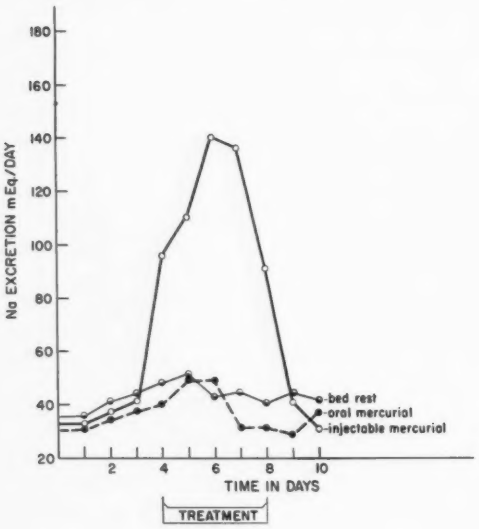
From the Department of Obstetrics and Gynecology, University of California at Los Angeles and the Department of Obstetrics and Gynecology, the Harbor County General Hospital, Los Angeles, Calif.

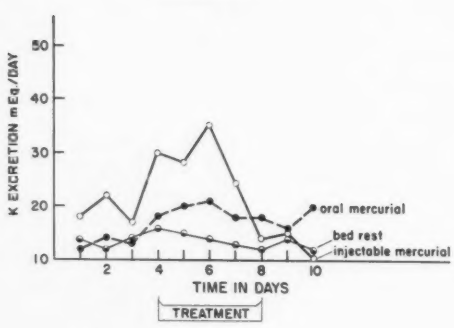
The investigation was supported in part by Grants from the National Heart Institute, National Institutes of Health, the Public Health Services.

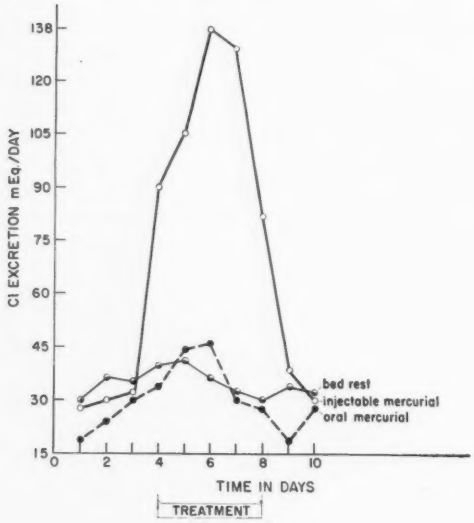
* Another group of 7 toxemic patients were studied during the administration of oral mercurials in doses smaller than the reported effective dose. Since no effects were observed, they were not included in this report.

† Neohydrin and Mercuhydrin were furnished through the courtesy of Lakeside Laboratories. Each tablet of Neohydrin contains 10 mg. of mercury so the total dose of mercury varied between 60 and 80 mg.

‡ Metrox and Mersoben were furnished by Ciba Pharmaceutical Products. Each tablet of Metrox contains 20 mg. of mercury so the total dose given of this compound varied between 120 and 160 mg. of mercury.







FIGS. 1–3

During each period, the patient's weight, blood pressure, and fluid intake and output were recorded daily. Arterialized blood samples were collected anaerobically without stasis from an antecubital vein after soaking the arm in warm water for 10 to 15 minutes. Twenty-four-hour urine specimens preserved with toluene and kept refrigerated were collected throughout the study and served for analyses of ammonia, titratable acids, and electrolytes. The completeness of urine collections was checked by the creatinine excretion. Plasma pH, carbon dioxide content, sodium, chloride, and potassium as well as urinary ammonia, titratable acids, and electrolytes were determined by methods previously described.[7]

RESULTS*

The administration of oral organomercurial drugs to either normally pregnant or toxemic patients resulted in a weight loss of 1 to 2 Kg. that was not regained after cessation of therapy. A slight increase in urine output along with a moderate increase in sodium, potassium, and chloride excretion was also observed, particularly during the Neohydrin administration. There was no change in either the plasma electrolytes or in blood pH or carbon dioxide. Similarly, urine pH and the excretion of ammonia and titratable acids remained the same. The patients with toxemia of pregnancy excreted significantly less electrolytes than those with normal pregnancy during the control period and continued to do so during the treatment period.

In the group of patients studied with bed rest alone, the changes in weight, urine output, sodium, potassium, and chloride excretion were similar to those observed during the administration of the oral mercurial compounds. Calculation of the significance of the differences be-

FIG. 1 *Top.* Sodium excretion in the urine induced by oral mercurials, bed rest, and injectable mercurials in patients with toxemia of pregnancy.

FIG. 2 *Middle.* Urinary potassium excretion during the administration of oral and injectable mercurials and bed rest. The difference between oral mercurials and bed rest was not significant.

FIG. 3 *Bottom.* Urinary chloride excretion produced by injectable and oral mercurials and by bed rest.

* Detailed data on changes in blood and urine compositions are listed in 8 tables that have been deposited with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress. Copies may be obtained from this Service (ADI document no. 5112) for $1.25, or from the author.

tween the mean of the groups of patients treated with oral mercurials and the means of the patients treated with bed rest was made by computing Student's t for each pair of values according to the method of Fisher.[8] The difference between bed rest and oral organomercurials was not significant ($p > .5$).

Intramuscular administration of organomercurial compounds resulted in a weight loss varying from 5 to 8 Kg. over the entire treatment period and the patients continued to lose weight after cessation of therapy. The loss of weight was mainly due to a marked increase in the excretion of water and electrolytes. The statistical difference between the means of the groups of patients given injectable organomercurials and the patients kept at bed rest was highly significant ($p = .001$) and so was the difference between injectable and oral organomercurials.

Figures 1–3 compare the effects of bed rest, and of oral and injectable mercurials on sodium, potassium, and chloride excretions. It is evident that the effects of bed rest and of oral mercurials were very close and they differ markedly from the effects of injectable mercurials irrespective of the type of mercurial compound utilized.

Side Effects. The side effects caused by oral administration of organomercurials were more conspicuous when 6 to 8 tablets were given. They consisted mostly of nausea, abdominal cramps, and in a few instances diarrhea and vomiting. These side effects, however, were not severe enough to warrant discontinuation of therapy.

Discussion

The present data show that the 2 oral organomercurial compounds did not have a significant diuretic action in normal and toxemic pregnancies and that the slight effects on weight and electrolyte excretion might have been due to bed rest. These results are in contrast to those obtained by Moyer and his coworkers[2, 3, 6] and by others[4, 5] in patients with cardiac edema, and by Dyer and his associates[9] in patients with toxemia of pregnancy. Moyer[6] found a significant weight reduction in ambulatory cardiac patients 2 days after the administration of 6 to 8 tablets of Neohydrin. However, no metabolic data were given by these authors and the conditions of the experiment were entirely different from those carried out here. The group of hospitalized patients studied by Dyer and his associates[9] were on a regime of salt restriction, bed rest, and other specific medications for toxemia, so that it would be difficult to state how much of the weight reduction was due to oral mercurials. Greiner and co-workers[10] assayed 3 oral organomercurials: 2 were found to be ineffective and 1 (Neohydrin) had one fourth of the activity of its injectable form. The patients studied by Greiner were also ambulatory in the outpatient department and reduction in weight was the only criterion of effectiveness utilized.

Two possible explanations could be given for the lack of striking results with oral organomercurials observed in the present study: (a) the dose was too small, and (b) pregnant patients have impairment in the intestinal absorption of mercury. The first hypothesis probably may be discarded, since the dose and mode of oral administration utilized here were not different from those used by others with the exception of Greiner.[10] This author administered the whole amount (1 to 9 tablets) as a single dose, so that the discrepancy between his and our results may be due to this difference in administration.

The second hypothesis receives support from the fact that intestinal absorption is known to be impaired in pregnancy due to the over-all hypotonicity of smooth muscles. So, it is possible that the fraction of mercury absorbed through the intestines was not sufficient to produce the desired diuresis. Studies on blood levels of mercury are in progress in order to elucidate this point.

The diuretic effects of injectable mercurials were certainly striking since, regardless of the preparation utilized, the patients invariably lost a significant amount of weight, mainly due to increased loss of water and electrolytes by the kidneys. Furthermore, despite the large dose employed, the side effects were practically nonexistent when the intramuscular route was employed. These properties of excellent diuretic action along with minimal side effects make injectable mercurials particularly suitable in the management of edema of pregnancy.

Nevertheless, the use of mercurials in obstetrics has been condemned by obstetricians on the theory that damage to the kidneys may occur and because the effects on the fetus are not known. In view of our observations and other reports[11] the fear of using mercurial diuretics in pregnancy does not seem well founded, in fact these agents may well be indicated in the cases of edema of pregnancy resistant to other simpler therapeutic regimens.

Summary

The diuretic effects of oral organomercurials (Neohydrin and Metrox) were compared to those induced by bed rest and by injectable mercurials (Mercuhydrin and Mersoben) in groups of normally pregnant and toxemic patients. No significant difference existed between the effects of oral mercurials and bed rest. Injectable mercurials produced marked diuretic effects, which were significantly different from those induced by oral mercurials and bed rest. It is suggested that the lack of diuresis of the oral mercurials might be due to impairment of intestinal absorption for mercury during pregnancy.

Summario in Interlingua

Le effectos diuretic de oral organomercuriales (Neohydrina e Metrox) esseva comparate con le effectos diuretic de allectamento e injicibile mercuriales (Mercuhydrina e Mersoben) in gruppos de gravidas normal e toxemic. Nulle significative differentias existeva inter le effectos de mercuriales oral e allectamento. Mercuriales del typo injicibile produceva marcate effectos diuretic que esseva significativemente differente ab le effectos inducite per mercuriales oral e per allectamento. Es formulate le possibilitate que le manco de diurese per mercuriales oral es explicabile per un obstruite absorption intestinal de mercurio durante le pregnantia.

References

[1] Pitts, R. F., and Sartorius, O. W.: Mechanism of action and therapeutic use of diuretics. J. Pharmacol. & Exper. Therap. Part II, **98:** 161, 1950.

[2] Moyer, J. H., Handley, C. A., and Wilford, L.: Results over a two year period on three experimental diuretics administered orally to patients with cardiac failure. Am. Heart J. **44:** 608, 1952.

[3] Silverthorne, C. C., and Moyer, J. H.: Diuretic effect of oral diethylaminoethyl-theophylline hydrochlorate used alone and with an oral mercurical compound in congestive heart failure. Fed. Proc. **12:** 367, 1953.

[4] Bresnick, E., and Abramson, J.: Clinical experiences with a new orally administered mercurial diuretic. New England J. Med. **249:** 681, 1953.

[5] Kaplan, B. M., Litman, I. H., Salarz, S. D., Miller, G., Mehlman, J. S., and Kaplan, L. G.: Clinical experience with a new oral mercurial diuretic, 3-chloromercuri-2-methoxypropylurea (1347 Ex). J. Lab. & Clin. Med. **42:** 269, 1953.

[6] Moyer, J. H., McConn, R. G., Seibert, R. A., Dennis, E. W., and Hughes, W.: A comparative study of Mersoben, Mercuhydrin (parenteral diuretics) Neohydrin, and Diamox (oral diuretics). J. Chron. Dis. **2:** 670, 1955.

[7] Assali, N. S., Monk, A., Ullrich, R., Voskian, J., and Singh, B. P.: Effects of inhibition of renal carbonic anhydrase by Diamox in normal and toxemic pregnancies. J. Lab. & Clin. Med. **46:** 733, 1955.

[8] Fisher, R. A.: Statistical Methods for Research Workers. Ed. 6, Edinburgh, Oliver and Boyd, 1936.

[9] Dyer, I., Hendrick, J. W., Lapointe, R., and Sewell, J.: Mercurial diuretics in toxemia of pregnancy (clinical use of "Neohydrin", an oral mercurial diuretic). Personal communication.

[10] Greiner, T., Gold, H., Palumbo, F., Warshaw, L., Weaver, J., Marsh, R., Mathes, S., and Kwit, N. T.: Human assay of three new mercurial diuretic agents: A promising preparation for oral use. Proc. Soc. Exper. Biol. & Med. **80:** 117, 1952.

[11] Brown, W. E., and Bradbury, J. T.: Relative effectiveness of various diuretics in causing sodium excretion in pregnant women. Am. J. Med. **3:** 127, 1947.

I observe the physician with the same diligence as he the disease.—John Donne, 1573–1631.

Significance of Pulmonary Elastic and Viscous Resistance in Orthopnea

By R. M. Cherniack, M.D., T. E. Cuddy, M.D., and J. B. Armstrong, M.D.

The mechanical properties of the lungs were measured in the sitting and supine positions in 5 normal subjects and in 5 patients with orthopnea due to congestive heart failure. The patients had higher elastic and viscous resistances in the sitting position. Recumbency increased both resistances in both groups but there was a disproportionate increase in the viscous resistance of the patients. This increase was most marked in late expiration and early inspiration. The significance of these findings to orthopnea is discussed.

THE mechanical properties of the lungs that oppose the action of the respiratory muscles consist of 2 types of resistance—elastic and viscous. Both are operative during lung movement but under static conditions only the elastic resistance is reflected in the pressure required to maintain any given state of inflation. During movement the viscous resistance comes into play and its additional effect on the pressure depends on both the resistance to air flow and the resistance to distortion of the nonelastic elements of the lung. Thus, by measuring the pressure differential across the lung under appropriate circumstances, it is possible to obtain estimates of both the elastic and viscous properties of the lung.

In 1917 Peabody[1] ascribed the dyspnea of congestive heart failure to an abnormality of the mechanical properties of the lungs. More recently orthopnea has been explained on a similar basis, an increase in the elastic resistance being thought to be an important factor.[2-5] The purpose of this paper is to report measurements of the elastic and viscous resistances in the erect and supine position. These show that the viscous resistance may be of greater consequence than the elastic in the genesis of orthopnea.

Method

The subjects were 5 normal individuals and 5 patients with congestive heart failure due to rheumatic or arteriosclerotic heart disease (table 1). At the time of study all patients had some degree of respiratory distress while lying down in addition to venous distention, basal pulmonary congestion, hepatomegaly, and peripheral edema. They also had a reduction in vital capacity and maximal breathing capacity as measured in the sitting position when compared to the predicted values calculated by the methods described by Baldwin, Cournand, and Richards.[6]

The mechanical properties of the lungs were measured and calculated by methods essentially the same as that previously described.[7] The effective intrathoracic pressure was measured by means of a strain-gage transducer connected on one side to an air-filled thin-walled latex balloon in the lower third of the esophagus and on the other side to the mouthpiece of a pneumotachometer (mesh stainless steel screen).

The rate of air flow into and out of the lungs was determined by measuring the pressure drop across the mesh stainless steel screen with a differential pressure strain-gage transducer (maximum range ±0.05 p.s.i.) Tracings of the air flow and esophageal-mouth differential pressure were recorded on a Sanborn Polyviso recorder. The volume of air breathed was determined by measuring the area under the pneumotachograph with a planimeter. The pneumotachometer was calibrated with rotameters and the pressure gage was calibrated with a water manometer after each study.

Simultaneous measurements of the pressure and volume changes from end expiration, determined at intervals of 0.2 second, were plotted one against the other during a complete breathing cycle. This plot produced a pressure volume loop from which the following information was derived.

Elastic Resistance. The pressure required to overcome the elastic resistance of the lungs during the breathing cycle was determined from the slope of a line joining the points of no flow at end expiration and end inspiration. The elastic properties of the lung were expressed as the index of elastic resistance, which is the number of centimeters of water static pressure change required to produce and maintain a change of 1 L. in lung volume.

From the Winnipeg General Hospital and the Department of Physiology and Medical Research, University of Manitoba, Winnipeg.

Supported by a grant from the National Research Council of Canada.

Drs. Cherniack and Armstrong are Markle Scholars in Medical Science; Dr. Cuddy is a Fellow, National Research Council of Canada.

TABLE 1.—*Clinical Data of Five Normal Subjects and Five Patients with Congestive Heart Failure*

Patient and age	Height (cm.)	Cardiac diagnosis*	Vital capacity (ml.)		M.B.C. (L./min.)	
			Predicted	Observed	Predicted	Observed
Normal subjects						
R. N., 33	178		4230	5580	124	150
B. B., 16	167		4200	3730	133	96
R. K., 24	178		4370	6260	132	154
H. J., 27	178		4430	5580	132	123
H. K., 21	173		4280	6070	132	194
Cardiac patients						
H. D., 67	170	AHD	—	—	—	—
L. L.,† 44	168	RHD	2950	2237	90	39
S. K., 70	173	RHD	3450	2802	82	73
E. H., 77	178	AHD	3530	2395	—	—
L. W., 66	168	AHD	3320	1160	75	33

* AHD—Arteriosclerotic heart disease; RHD—Rheumatic heart disease.

† Female, all others male.

Viscous Resistance. The pressure required to overcome viscous resistance at any particular time during a respiratory cycle was ascertained from the pressure-volume loop by subtracting from the intrathoracic pressure the pressure required to overcome the elastic resistance at that instant. The pressures developed against the viscous resistance were plotted against simultaneously recorded rates of air flow and the pressure existing at flow rates of 30 L. per minute was chosen to express the viscous resistance.

Work of Breathing. The area of the pressure-volume loop represented the mechanical work done on the lungs in order to overcome viscous resistance and was expressed in kilogram centimeters.

The mechanical work required to overcome elastic resistance was obtained from the area of the right-angled triangle whose hypotenuse was formed by the line joining the points of end expiration and end inspiration as described by McIlroy, Marshall, and Christie,[8] and was expressed in kilogram centimeters.

The total work done on the lungs was calculated by adding the elastic work, the inspiratory viscous work, and the portion of the expiratory viscous work that fell outside the elastic work area.

The work per minute was calculated by multiplying the work per breath by the respiratory rate.

TABLE 2.—*Index of Elastic Resistance and the Viscous Resistance in Five Normal Subjects and Five Patients with Congestive Heart Failure in Sitting and Supine Positions*

Subject	Index of elastic resistance (cm. H_2O/L.)		Viscous resistance pressure (cm. H_2O) to produce flow 30 L./min.					
			Sitting		Supine*			
	Sitting	Supine	Insp.	Exp.	Insp.		Exp.	
					Low	High	Low	High
Normal subjects								
R. N.	5.99	6.76	0.6	1.0	0.4	0.9	1.9	1.8
B. B.	9.34	12.50	1.1	1.4	1.3	1.2	2.0	2.3
R. K.	4.20	5.46	1.2	1.1	1.7	1.7	2.7	3.1
H. J.	7.82	11.10	0.9	0.9	1.3	1.2	1.1	1.2
H. K.	3.52	6.50	0.6	0.8	1.2	1.0	1.2	0.9
Mean	5.40	8.46	0.9	1.0	1.15	1.2	1.8	1.8
Cardiac patients								
H. D.	10.86	21.74	1.2	1.4	4.25	1.15	6.8	1.7
L. L.	11.5	14.92	3.2	4.1	5.9	3.2	8.8	5.2
S. K.	7.94	9.62	1.8	2.2	5.1	1.7	9.1	2.0
E. H.	10.75	11.00	1.3	2.2	2.6	0.6	5.5	2.0
L. W.	21.30	15.40	1.5	2.4	2.35	2.15	4.4	1.9
Mean	12.47	15.54	1.8	2.5	4.0	1.8	6.9	2.6

* Viscous resistance in the supine position is shown separately at high and low levels of lung inflation because of the marked effect of lung expansion on the viscous resistance seen in the supine cardiac patients.

The index of elastic resistance was calculated rom the average of 10 to 20 breaths. Viscous resistnce and the work done on the lungs were calculated rom the average of 4 to 5 breaths.

The subjects were studied in the sitting position nd again 5 to 15 minutes after the assumption of he supine position. Patient L. W. was an exception n that he was supported at an angle of 30 degrees ecause of his inability to lie flat.

Results

Elastic Resistance. Table 2 shows that in the sitting position the index of elastic resistance was higher in the patients with congestive heart failure than in the normal subjects. Assumption of the supine position increased its value in all the normal and in 4 of the 5 cardiac subjects, the fifth being unable to lie flat.

Viscous Resistance. It will be seen in table 2 that the viscous resistance in the sitting position was higher in the cardiac than in the normal subjects. Figure 1 shows that this was true at all rates of air flow. The greater viscous resistance in the cardiac patients is indicated by the greater pressure required to produce a given flow.

On lying down, an increase in viscous resisttance occurred in both groups of subjects (table 2). In normal subjects the increase was spread uniformly over the respiratory cycle but in patients with congestive heart failure the increase was not uniform, being particularly marked at the beginning of inspiration and at the end of expiration. The relationship of viscous resistance to the respiratory cycle in the supine position is shown in figure 2 for the same subjects as shown in figure 1. It will be seen that in the cardiac patient a greater pressure was required to produce a given flow at the beginning of inspiration than was required as inspiration progressed. In expiration, a lower pressure was required at the beginning of expiration than was required as expiration progressed. The data in table 2 indicate that this was true for all the cardiac patients and was not apparent in the normal subjects.

Work of Breathing

In the sitting position the work performed on the lungs against both the viscous and elastic resistances was greater for the cardiac than the normal subjects (table 3). Similarly, the total work of breathing was much greater in the cardiac than in the normal subjects.

The assumption of the supine position did not result in an increase in the elastic work of breathing in either group, as a decrease in minute volume offset the increase in the index

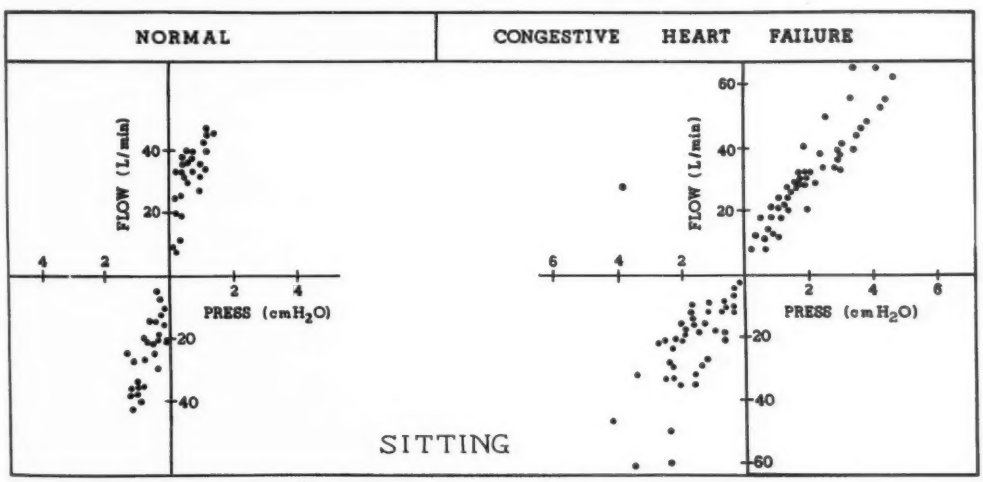


Fig. 1. Viscous pressure-flow curves for a typical normal subject (H. K.) and a patient with congestive eart failure (S. K.) measured in the sitting position. Data from 4–5 breaths. (Inspiration is represented in the pper right quadrant, expiration is represented in the lower left quadrant.)

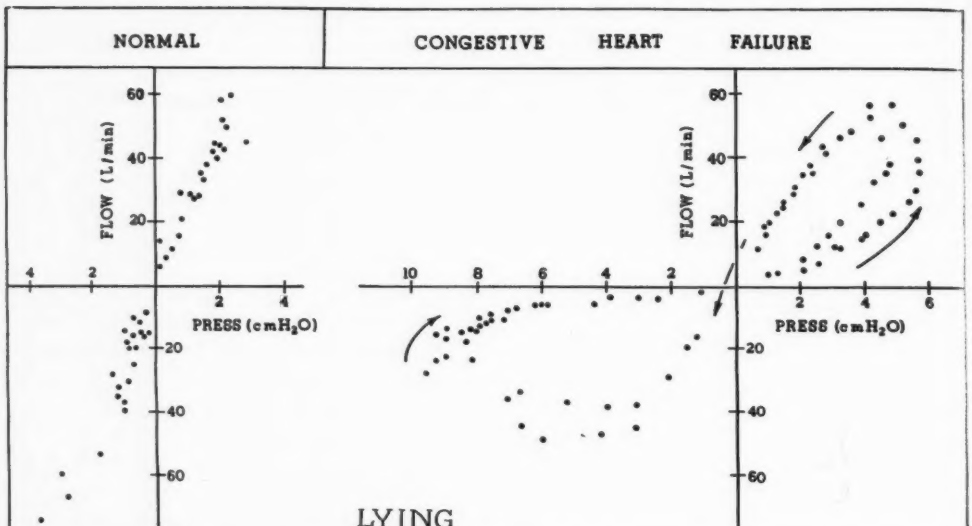


FIG. 2. Viscous pressure-flow curves in the supine position for the same patients shown in figure 1. Data from 4–5 breaths. (Inspiration is represented in the upper right quadrant; expiration in the lower left quadrant.)

TABLE 3.—*Work of Breathing of Five Normal Subjects and Five Patients with Congestive Heart Failure Measured in the Sitting and Supine Positions*

Subject	Work of Breathing (Kg. cm./min.)					
	Elastic		Viscous		Total	
	Sitting	Supine	Sitting	Supine	Sitting	Supine
Normal subjects						
R. N.	26.4	27.1	26.9	27.9	39.9	41.1
B. B.	11.0	17.2	25.6	17.2	23.8	25.8
R. K.	39.6	34.9	49.6	92.4	64.4	81.1
H. J.	49.4	34.9	39.2	40.9	69.0	55.4
H. K.	32.2	40.7	18.9	37.5	41.7	59.5
Mean	31.7	31.0	32.0	43.2	47.8	52.5
Cardiac patients						
H. D.	57.8	87.6	101.4	152.0	123.7	186.3
L. L.	58.0	66.1	99.0	132.5	122.4	152.1
S. K.	39.2	40.0	36.3	122.5	62.8	119.6
E. H.	120.1	94.9	140.6	180.2	211.6	211.9
L. W.	40.9	35.6	53.8	72.9	75.9	82.0
Mean	63.2	64.4	86.2	132.0	119.3	150.4

of elastic resistance shown in table 2. The main effect of recumbency was to increase the work required to overcome viscous resistance. The average increase was approximately 30 per cent in the normal subjects while in those with congestive failure it was over 50 per cent of the already very high value. Consequently in the supine position the total work of breathing tended to be increased in both groups but the effect was most pronounced in the cardiac patients. It is of interest that the one patient (L.W.) who could not lie flat, did not have an increase in elastic resistance or elastic work but did have a marked increase in viscous resistance and viscous work.

DISCUSSION

The results of this study confirm the observations of others[9-11] that elastic and nonelastic resistance is elevated in congestive heart failure in the sitting position. This is presumably related to the increased pulmonary blood volume believed to be present in this condition.[12, 13]

The assumption of the supine position resulted in an increase in the viscous resistance and viscous work of breathing that was more pronounced than the increase in elastic resistance and elastic work of breathing. This was particularly marked in patients with congestive heart failure. It is logical, therefore, to relate

orthopnea to the increase in viscous resistance induced by the assumption of the supine position.

An explanation of the effect of the recumbent position on the viscous resistance of the lungs must include an explanation of the peculiar relationship of this resistance to the state of lung inflation. A similar but less marked effect of lung inflation has been observed in normal subjects while breathing in an expiratory position or during forced expiration and in emphysematous subjects during expiration.[14] These observations suggest that the high viscous resistance at low lung volumes is due to narrowing of the air passages in this state. Patients with congestive heart failure in the supine position would be especially likely to show this phenomenon because of congestion and edema tending to obstruct the air passages. As the lungs expand these passages would be opened, lowering the resistance to air flow.

In assessing the effect of recumbency on respiration, consideration should be given to the fact that the brunt of the increase in viscous resistance fell in late expiration and early inspiration. It is believed that this concentration of the resistance to breathing on one part of the respiratory cycle would have a more disturbing effect than if its equivalent were spread over the whole cycle. If this be true, the values for the work of breathing reported in table 3 underestimate the adverse effect of recumbency. In any case, the values show that the total work of breathing of the supine cardiac patient was approximately 25 per cent greater than that of the sitting cardiac patient and that this difference was attributable to the difference in the work against viscous resistance.

Summary

The assumption of the supine position resulted in a marked increase in viscous resistance in patients with congestive heart failure. The major part of this increased resistance occurred at the end of expiration and beginning of inspiration when lung volumes were low. As a consequence, the work of breathing in patients with congestive heart failure in the supine position was increased by 25 per cent. The dyspnea of recumbency in these patients is tentatively attributed to interference with the patency of the respiratory passages at low levels of lung inflation.

Acknowledgment

The authors wish to thank Mrs. T. E. Cuddy and Miss A. Grassler for valuable technical assistance.

Summario in Interlingua

Post prender un position decubital, patientes con congestive disfallimento cardiac manifestava marcate augmentos del resistentia viscose. Le major portion de iste augmentos occurreva al fin del expiration e al comenciamento del inspiration quando le volumine pulmonar esseva basse. In consequentia de isto, le labor respiratori in patientes con congestive disfallimento cardiac esseva augmentate per 25 pro cento durante que illes se trovava in un position decubital. Le dyspnea decubital in iste patientes es tentativemente attribuite al obstruction del libere passage in le vias respiratori a basse nivellos del inflation pulmonar.

REFERENCES

[1] Peabody, F. W.: Clinical studies of respiration. III. A mechanical factor in the production of dyspnoea in patients with cardiac disease. Arch. Int. Med. **20:** 433, 1917.

[2] Hamilton, W. F., and Morgan, A. B.: The mechanism of postural reduction in vital capacity in relation to orthopnoea and storage of blood in the lungs. Am. J. Physiol. **99:** 526, 1932.

[3] Christie, R. V., and Meakins, J. C.: The intrapleural pressure in congestive heart failure and its clinical significance. J. Clin. Invest. **13:** 323, 1934.

[4] Prinzmetal, M., and Kountz, W. B.: Intrapleural pressure in health and disease and its influence on body function. Medicine **14:** 457, 1935.

[5] Christie, R. V.: Dyspnoea in relation to viscoelastic properties of the lungs. Proc. Roy. Soc. Med. **46:** 381, 1953.

[6] Baldwin, E. deF., Cournand, A., and Richards, D. W.: Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine **27:** 243, 1948.

[7] CHERNIACK, R. M.: The physical properties of the lung in chronic obstructive pulmonary emphysema. J. Clin. Invest. **25:** 394, 1956.

[8] MCILROY, M. B., MARSHALL, R., AND CHRISTIE, R. V.: The work of breathing in normal subjects. Clin. Sc. **13:** 127, 1954.

[9] MARSHALL, R., MCILROY, M. B., AND CHRISTIE, R. V.: The work of breathing in mitral stenosis. Clin. Sc. **13:** 137, 1954.

[10] BROWN, C. C., FRY, D. L., AND EBERT, R. V.: The mechanics of pulmonary ventilation in patients with heart disease. Am. J. Med. **17:** 438, 1954.

[11] MEAD, J., FRANK, N. R., LINDGREN, I., GAENSLER, E. A., AND WHITTENBERGER, J. L.: A technique for the measurement of pulmonary compliance and resistance, its application to normal patients and patients with mitral stenosis. Clinical Research Proceedings **1:** 116, 1953.

[12] BORDEN, C. W., EBERT, R. V., WILSON, R. H., AND WELLS, N. S.: Studies of the pulmonary circulation II. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs of patients with mitral stenosis and in patients with left ventricular failure. J. Clin. Invest. **28:** 1138, 1949.

[13] KOPELMAN, H., AND LEE, G. DEJ.: The intrathoracic blood volume in mitral stenosis and left ventricular failure. Clin. Sc. **10:** 383, 1951.

[14] MEAD, J., LINDGREN, I., AND GAENSLER, E. A.: The mechanical properties of the lungs in emphysema. J. Clin. Invest. **34:** 1005, 1955.

Denison, A. B., Jr., Bardhanabaedya, S., and Green, H. D.: Adrenergic Drugs and Blockade on Coronary Arterioles and Myocardial Contraction. Circulation Research **4:** 653 (Nov.), 1956.

Although epinephrine, norepinephrine, and isopropylarterenol caused markedly different vasomotor responses in many vascular beds, their effects on the coronary bed were qualitatively similar. All 3 amines caused dilatation of the coronary vessels, as measured by decreases in resistance to blood flow measured by an electromagnetic flowmeter (cannulated anterior descending ramus of dog). It was conspicuous that all of them increased myocardial contraction as estimated from the effects on flow during isometric contraction, resistance at systole, and amplitude of the intracoronary systolic pressure. The greater effectiveness in hypotensive states of norepinephrine, as compared with epinephrine, would appear to be due to differences in their systemic rather than their cardiac effects, since the direct effects on the myocardium were similar.

AVIADO

Stenosis of a Branch of the Pulmonary Artery

An Additional Cause of Continuous Murmurs over the Chest

By Frederic Eldridge, M.D., Arthur Selzer, M.D., and Herbert Hultgren, M.D.

Three patients have been demonstrated by cardiac catheterization to have stenosis of a main branch of the pulmonary artery. Two exhibited continuous ductus-like murmurs at the chest wall over the site of stenosis. Demonstration of a pressure gradient throughout the cardiac cycle at the site of stenosis in these 2 patients and the experimental production in the dog of a continuous murmur at the site of partial constriction of a pulmonary artery prove that the murmur is due to the stenosis. This anomaly should be added to the differential diagnosis of continuous murmurs over the chest.

STENOSIS of a main branch of the pulmonary artery has been previously considered very rare. Bredt[1] and Mönckeberg[2] believed that it never occurred independently of stenosis of the pulmonary orifice. Schwalbe[3] in his comprehensive survey of malformations referred to 4 reported instances, but a review of the original reports reveals only 2 in which narrowing of a branch of an otherwise normal pulmonary artery was present,[4, 5] the other 2 being patients with absence of either the right or left pulmonary artery. In 1938 Oppenheimer[6] reported a stricture of the right pulmonary artery and of the lower branch of the left pulmonary artery in a 17-month-old infant. Four patients with stenosis at the area of the bifurcation of the pulmonary artery and insertion of the ligamentum arteriosum have been discovered at operation by Schumaker and Lurie[7] and Søndergaard.[8] Kjellberg and his associates[9] mention having seen a case of supravalvular stricture of the main pulmonary artery. Arvidsson and his associates[10-12] recently reported 4 patients with pulmonary hypertension in whom multiple stenoses of the main branches of the pulmonary artery were demonstrated by selective angiography. In 1 of these patients a continuous murmur was present over the upper chest.

In this communication 3 additional patients with stenotic lesions of the main branches of the pulmonary artery are described including 2 patients manifesting continuous murmurs. Experimental evidence is also presented that a continuous murmur can be produced by constriction of the main branches of the pulmonary artery.

From the Department of Medicine of the Stanford University School of Medicine, San Francisco, Calif.

Frederic Eldridge and Herbert Hultgren are Scholars in Medical Science of the John and Mary R. Markle Foundation.

Case Reports

Case 1. G.T., a 7-year-old Negro girl, entered the Stanford University Hospital in February 1956 with the history of a heart murmur and congenital absence of the right radius having been noted at the age of 1 year. She had been asymptomatic except for several episodes of pneumonitis.

She was an alert, active girl. Her brachial blood pressure was 94/66 mm. Hg. There was shortening and radial deviation of the right forearm. The lungs were clear. The heart was regular. At the pulmonic area the second sound was loud and slightly split. There was a grade III murmur filling systole over the left precordium, and a loud continuous murmur of grade IV intensity was heard at the right second intercostal space just medial to the midclavicular line. This murmur was well transmitted to the right axilla and back.

The urinalysis and blood count were not remarkable. The electrocardiogram showed high voltage R waves over the right precordium, compatible with right ventricular hypertrophy. X-ray pictures showed marked pulmonary plethora, right ventricular enlargement, and widening of the superior mediastinum. A phonocardiogram (fig. 1) demonstrated a continuous murmur over the second intercostal space, just medial to the right midclavicular line and a loud, slightly split second sound in the pulmonic area. The continuous murmur was essentially similar to the machinery murmur produced by the usual uncomplicated patent ductus. The murmur appeared about 0.06 second after the peak of the apical first sound, increased to maximal intensity just before or at the time of the second sound, and faded away in diastole. The diastolic component

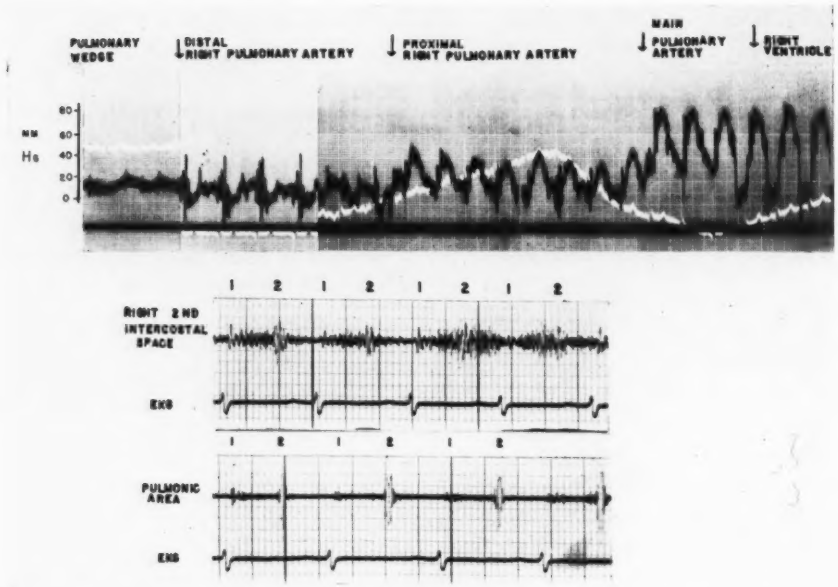


FIG. 1. *Case 1.* The top tracing shows pressures obtained during withdrawal of the cardiac catheter from right lung. The pressure in the distal right pulmonary artery shows a systolic dip due to the Venturi effect. Next is a sharp rise in pressure as the catheter tip is withdrawn to the proximal right pulmonary artery, and then a further sharp rise of pressure in the main pulmonary artery. Both sharp rises of pressure indicate sites of stenosis. The lower 2 tracings are phonocardiograms showing the continuous murmur heard in the right second intercostal space and the heart sounds as heard in the pulmonic area. The first and second heart sounds are shown on both tracings by the numbers 1 and 2.

appeared to diminish in intensity readily during expiration.

Cardiac catheterization revealed a high oxygen saturation in the superior vena cava (86 per cent) and the right atrial oxygen saturation was higher than that in the inferior vena cava. In addition, there were arterial anoxemia, moderate pulmonary hypertension, and at least 2 sites of stenosis in the right main pulmonary artery (table 1 and fig. 1). The pressure tracing recorded during the withdrawal of the catheter from the wedged position revealed first a typical, normal, wedged-pressure tracing (fig. 1, far left), then an abrupt change in the pressure curve with a distinct dip in pressure during systole and then an abrupt increase in pressure with a positive pressure pulse during systole, and finally a second abrupt rise in pressure. The systolic dip in the pressure trace is probably due to the blood flow through the constricted vessel producing a Venturi effect, such as is occasionally seen when the catheter tip is at the stenotic orifice in valvular pulmonic stenosis.[13, 14] This portion of the tracing and the 2 abrupt rises in pressure in the pulmonary artery conclusively establish the presence of 2 areas of stenosis in the right branch of the pulmonary artery.

Venous angiocardiography subsequently confirmed the presence of a total anomalous pulmonary venous return to the right atrium by means of a persistent left superior vena cava, and demonstrated a moderate dilatation of the right pulmonary artery. The first portion of the right pulmonary artery was poorly seen on the film because it was located over the spine. No distinct area of stenosis could be seen.

Comment. This patient had multiple congenital anomalies. Two sites of stenosis of the pulmonary artery were demonstrated by catheterization. The continuous murmur was located directly over the point where the stenosis of the right main pulmonary artery was demonstrated. The quality of the murmur was quite unlike that of a venous hum, which has been occasionally described over the area of insertion of anomalous pulmonary veins into the right atrium or venae cavae.[15] The rise in the intensity of the murmur a short interval after the first heart sound and the decrease in intensity during diastole correspond to the phasic

TABLE 1.—*Catheterization Findings in Case 1*

	Oxygen content, ml./100 ml.	Pressure, mm. Hg
Left axillary vein	16.0	
Superior vena cava*	15.7	
Inferior vena cava	11.5	
Right atrium*	13.5	9 (mean)
Right ventricle*	13.6	82/11
Main pulmonary artery*	13.6	82/29
Left pulmonary artery	13.9	89/29
Proximal right pulmonary artery	13.8	39/13
Distal right pulmonary artery	14.0	19/8
Pulmonary artery wedge	—	14 (mean)
Femoral artery	13.9	
Arterial oxygen saturation	77%	

* These figures represent the average value of 2 or more samples.

FIG. 2. Case 2. Phonocardiogram taken in the pulmonary area showing the systolic ejection murmur and the diastolic murmur. The location of the heart sounds is shown by the numbers 1 and 2.

pressure changes recorded from the pulmonary artery at the point of the demonstrated stenosis.

Case 2. R.W., a 7-year-old boy, was first seen at the Stanford University Hospital at the age of 6 months, when he was noted to have a thrill at the fourth intercostal space along the left sternal border and a loud systolic murmur in the same area. At the pulmonic area a systolic murmur of grade III intensity was followed by a short early diastolic murmur. While not a truly continuous murmur, several observers believed it so on the basis of auscultation alone, and a diagnosis of a probable patent ductus arteriosus was made. At the age of 2 years a thoracotomy was performed at this hospital. The surgeon discovered a small ligamentum arteriosum and ligated it. There were no changes in the murmurs following this surgery.

The patient remained asymptomatic and again entered the hospital at the age of 7½ years for further studies. He appeared well. His brachial blood

TABLE 2.—*Catheterization Findings in Case 2*

	Oxygen content, ml./100 ml.	Pressure, mm. Hg
Superior vena cava	13.2	
Inferior vena cava	12.5	
Right atrium*	12.0	2 (mean)
Right ventricle*	13.5	20/3
Main pulmonary artery	13.9	21/6
Right pulmonary artery	13.3	21/6
Left pulmonary artery	—	15/8
Femoral artery	15.0	115/60
Arterial oxygen saturation	91%	

* These figures represent the average of 2 or more samples.

TABLE 3.—*Catheterization Findings in Case 3*

	Oxygen content, ml./100 ml.	Pressure, mm. Hg
Superior vena cava	10.6	
Inferior vena cava	11.0	
Right atrium*	12.6	7 (mean)
Right ventricle*	12.3	42/8
Main pulmonary artery	12.6	38/10
Left pulmonary artery	—	41/9
Right pulmonary artery	12.2	20/8
Femoral artery	14.0	94/50
Arterial oxygen saturation	87%	

* These figures represent the average of 2 or more samples.

pressure was 98/60 mm. Hg. There was a systolic thrill and a harsh grade IV systolic murmur loudest at the left sternal border in the fourth intercostal space. In the pulmonic area a grade III systolic murmur was immediately followed by a grade III diastolic murmur of diminishing intensity during diastole.

Routine laboratory studies were normal. The electrocardiogram revealed somewhat high QRS voltage over the precordium but was otherwise normal for a child of 7 years. X-rays showed somewhat prominent right and left ventricles and a large main pulmonary artery. The pulmonary vasculature was prominent. A phonocardiogram (fig. 2) revealed a loud crescendo systolic murmur compatible with a shunt through an interventricular septal defect. At the pulmonic area a systolic ejection murmur with its maximum intensity in midsystole was recorded. It was followed by a murmur of lesser intensity continuing into diastole.

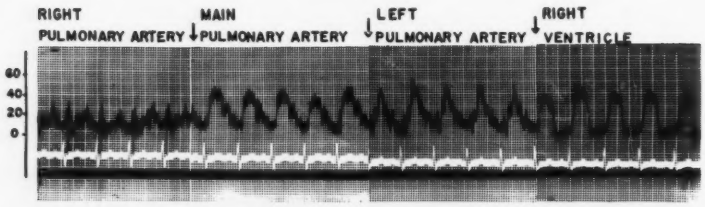


FIG. 3. Pressures obtained at cardiac catheterization in case 3. There is a rise in pressure between the right pulmonary artery and the main pulmonary artery indicating the site of the stenosis.

Cardiac catheterization was performed and indicated a ventricular septal defect with a small left-to-right shunt (table 2). During the procedure it was noted that the catheter passed in an unusual fashion posteriorly and laterally into the left pulmonary artery and that there was a definite sudden pressure drop in this portion of the left main pulmonary artery (table 2).

Comment. The ventricular septal defect was the principal cardiac lesion in this case. The stenosis of the left pulmonary artery was an incidental finding, and was probably the cause of the systolic and diastolic murmur closely resembling a continuous murmur that had previously led to a surgical exploration for a patent ductus arteriosus. Since the murmur was present before the thoracotomy, it is unlikely that the operation produced the narrowing of the pulmonary artery. It is of interest that pulmonary hypertension was not present.

Case 3. J.C., a 5-year-old boy, was examined in April 1956. A heart murmur had been heard at birth but he had developed normally and had experienced no symptoms except questionable easy fatigability.

He looked well. His brachial blood pressure was 100/60 mm. Hg. There was a slight precordial bulge of the left chest wall parasternally. A thrill and a grade IV systolic murmur were present along the left sternal border in the third and fourth intercostal spaces. The pulmonic second sound was loud.

Routine laboratory studies were not unusual. The electrocardiogram revealed a pattern consistent with incomplete right bundle-branch block, right ventricular hypertrophy, and abnormal P waves. X-ray studies revealed a prominent main pulmonary artery, increased pulmonary vascularity, and enlarged right and left ventricles.

Cardiac catheterization demonstrated an atrial septal defect with a left-to-right shunt (table 3) and mild pulmonary hypertension. In addition, there was a definite drop of systolic pressure in the right pulmonary artery 4 to 5 cm. beyond the bifurcation of the main pulmonary artery (fig. 3) indicating the presence of a stenosis of the right pulmonary artery. Mild arterial unsaturation was thought to be due to hypoventilation accompanying the tribromoethanol (Avertin) anesthesia.

Comment. The atrial septal defect was the principal lesion in this patient. Since a continuous murmur was not present, there appears to be nothing in the clinical findings that would enable one to make the diagnosis of stenosis of the right pulmonary artery.

DISCUSSION

The exact nature of such stenotic lesions involving the pulmonary artery distal to the valve is obscure because of the rarity of such lesions and the paucity of descriptions of their pathologic anatomy. Partial obstruction by thrombosis or embolus or a congenital developmental defect are the 2 most likely possibilities.

Partial occlusion by thrombosis, secondary to trauma of the chest wall, of the main pulmonary artery in an adult has been described by Dimond and Jones.[16] The resulting clinical picture resembled that of pulmonary stenosis with an intact septum. Pulmonary thrombosis or embolism with partial recanalization could result in single or multiple areas of narrowing of the branches of the pulmonary artery; since resorption of an occluding thrombus or embolus may be variable, complete restitution of the lumen may occur or a residual area of stenosis may remain.[17, 18] Saphir,[19] for example, has concluded that small bands or valvelike structures found occasionally in the pulmonary artery represent vestiges of resorbed mural thrombi. Partially resorbed multiple thrombi or emboli similar to those illustrated in Møller's paper[17] could easily give the curious rounded or scalloped appearance demonstrated so clearly in the angiograms of one of Arvidsson's pa

tients[12] (case 1). However, it seems unlikely that this was the etiology of the stenotic lesions present in our patients, for there was no clinical history compatible with pulmonary thrombosis or embolism. Although such a process could have occurred during intra-uterine development, there are no descriptions in the literature of any such lesions in the fetus or newborn.

A developmental, congenital defect of the pulmonary artery seems more likely. The occurrence in childhood, the association with other congenital cardiac lesions, and the absence of any evidence of an acquired etiologic process all suggest this possibility. Søndergaard[8] suggested that the cause of stenosis of the pulmonary artery at its bifurcation was due to the incorporation of the pulmonary artery by the tissue of the closing ductus arteriosus (the Skodaic theory). This theory was first suggested by Craigie[20] and later supported by Skoda to account for the origin of the adult type of coarctation of the aorta. Although one of the patients in the present report (case 2) probably had a single area of stenosis at the bifurcation, such a theory would not explain the stenosis of the more peripheral branch of the right pulmonary artery (case 3) and the multiple stenoses observed in case 1.

The only detailed report of a patient with stenosis of the main branches of the pulmonary artery in which a complete autopsy study was described is by Oppenheimer.[6] In that 17-month-old child, the right pulmonary artery and the lower branch of the left pulmonary artery were constricted by thickened intimal tissue beneath which were extensive deposits of calcium in the media. The right pulmonary artery at the stenotic area was completely encircled by a ring of calcium. Calcification was also present in the media of the aorta. Five other instances of calcification of the pulmonary artery were described but in none of these patients was there any narrowing of the pulmonary arteries. The author suggested a congenital origin for these lesions. It is possible that a similar process is present in our patients, but a careful review of the x-ray studies revealed no evidence of calcifications either in the pulmonary arteries or aorta.

The question of the proper terminology of such lesions of the pulmonary artery should be considered. Søndergaard[8] suggested the term "coarctation of the pulmonary artery" because of the resemblance in structure and, as he believed, in origin to the adult variety of aortic coarctation. This term would be desirable if the stenosis were isolated and located near the bifurcation and if the Skodaic theory were the proper explanation for such a lesion. Many of these lesions are multiple, however, and they may be located at various points in the pulmonary artery. Furthermore, the Skodaic theory of the origin of the adult variety of coarctation of the aorta has been attacked for compelling reasons by Edwards and associates,[21] and the possibility of such a process being the cause of a stenosis of the pulmonary artery is only conjectural. Oppenheimer[6] referred to the lesions as "partial atresia of the main branches of the pulmonary artery." This is a poor term because atresia means "without a lumen," hence it cannot be partial. Considering the fact that such areas of narrowing may occur at many sites in the pulmonary artery distal to the valve, that they may be multiple, and that their exact origin is still unknown, it might be best to refer to them as "stenoses of the pulmonary artery" specifying the area involved, i.e., "stenosis of the main pulmonary artery, stenosis of the right or left pulmonary artery, etc."

Arvidsson and co-workers[12] suggested that this anomaly may be the cause of hypertension in the main pulmonary artery. The fact that in 2 of their patients with multiple stenoses no other anomaly was demonstrated suggests that this may be the case; but such a relationship is by no means certain. It should be pointed out that abundant clinical and experimental evidence is available to show that even total occlusion of 1 main pulmonary artery does not increase the resistance enough to elevate pulmonary arterial pressure if the flow is not increased and if the pulmonary vascular bed is normal. Localized narrowing would be even less likely to cause pressure rise per se, unless both branches were involved. Furthermore, in 2 cases of the 3 reported here, in which pulmonary hypertension was present, there existed another congenital defect (anomalous venous return and ven-

tricular septal defect) which in itself may be associated with pulmonary hypertension.[15]

The physiologic effects of stenosis of a main branch of the pulmonary artery are not readily apparent unless a relationship to pulmonary hypertension can be demonstrated. No measurements of relative blood flow to the lungs have been made, although on theoretic grounds one might expect some changes from the normal.

In one of the reported cases the stenotic area was dilated surgically[7] and clinical improvement was thought to have taken place. Whether surgical intervention for the sole purpose of dilating a localized stenosis of a pulmonary arterial branch is justified, cannot be answered on the basis of information at hand. One is inclined, however, to lean toward the view that this is a benign, clinically insignificant lesion that would not justify thoracotomy under ordinary circumstances.

Unfortunately, there are no distinctive clinical signs of the presence of stenosis of the main branches of the pulmonary artery, unless a continuous murmur be present. In order to detect such lesions during cardiac catheterization, both branches of the pulmonary artery should be entered and withdrawal tracings recorded from each branch. Since continuous murmurs are produced by this lesion only when the degree of stenosis is severe, one might expect the murmur to be extinguished or suddenly changed in intensity when the catheter is passed through the area of narrowing.

The most apparent significance of stenosis of a main branch of the pulmonary artery lies in its relationship to the origin of continuous murmurs. Continuous, ductus-like murmurs have been observed in 3 cases: in 1 patient of Arvidsson[12] and in 2 reported here. The location of the continuous murmur over the thorax at the site of the stenosis and the appearance of the phonocardiogram suggest strongly that the murmur originated at the stenosis. It was thought, however, that in order to prove this relationship beyond doubt, an examination of the nature of the pressure gradient across the stenotic areas should be made and an experimental reproduction of such a murmur would have to be accomplished.

Several conditions must be fulfilled for a continuous murmur of this sort to be produced. There must be narrowing of the blood channel and sufficient flow through the constricted area to produce turbulence during both systole and diastole. In order to have flow in diastole of sufficient volume and velocity to produce this turbulence, a reservoir of blood under pressure must exist proximally to the constriction. These conditions are met in the case of patent ductus arteriosus, peripheral and pulmonary arteriovenous fistulas, and in some of the more unusual arteriovenous communications. They are also met in the case of stenosis of a pulmonary artery branch where the proximal pulmonary arterial bed acts as the reservoir under pressure.

The presence of a sufficient volume and velocity of blood flow to produce turbulence can best be demonstrated by showing a pressure gradient between the areas proximal and distal to the narrowed area. Such a gradient can easily be demonstrated, both in systole and diastole, between the aorta and the pulmonary artery in a typical case of patent ductus arteriosus with continuous murmur. Furthermore, it has been shown that when pulmonary hypertension develops, leading to an obliteration of the gradient in diastole or in both systole and diastole, there is disappearance of the diastolic component of the murmur in the first instance and total disappearance of the murmur in the second.[24] Figure 4 shows the gradients of pressure for 1 cardiac cycle across the areas of stenosis in the 3 patients presented in this report. The pressure gradients were constructed from an analysis of the pressure curves obtained proximally and distally to the area of pressure drop. Significantly, the 2 patients with continuous murmurs showed a gradient throughout the entire cycle, whereas the third patient, in whom only a systolic murmur was observed, showed a pressure gradient only in systole. This is offered as evidence that the continuous murmur heard in 2 of our cases originated at the site and was caused by the stenosis of the pulmonary artery. It also explains why such a murmur is present in some cases only.

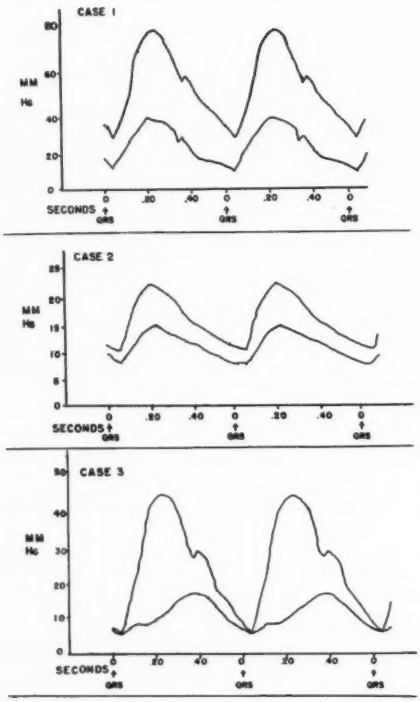


FIG. 4. Graph of pulmonary artery pressures proximal (upper curve in each case) and distal (lower curve in each case) to area of stenosis, showing pressure gradients across the stenosis during the heart cycle.

EXPERIMENTAL STUDY

The experimental part of our study was performed in acute experiments on dogs anesthetized with intravenous pentobarbital. A special constricting clamp[22] was placed around a large branch of the pulmonary artery and graded constriction applied. Auscultation of the constricted area revealed only a faint systolic murmur. In the next experiment the constricting clamp was placed around the thoracic aorta and graded constriction applied. One could observe and register phonocardiographically a soft systolic murmur with mild constriction, a loud systolic murmur with more severe constriction, then a continuous murmur, first with a faint diastolic phase, and upon further constriction a loud murmur throughout the cardiac cycle. A similar series of experiments, performed independently, was recently reported by Myers and associates.[23] In the final experiment it was thought that if a branch of the pulmonary artery could be constricted and the flow through it increased, a situation similar to that in the thoracic aorta would arise. In this experiment the clamp was placed around the superior branch of the left pulmonary artery (the main branch in the dog is too short before its bifurcation to place a clamp around it) and graded constriction was applied after completely clamping the right pulmonary artery. In this experiment mild constriction of the left pulmonary artery produced a systolic murmur and more severe constriction produced a continuous murmur similar to that of aortic constriction (fig. 5).

The experimental reproduction of a continuous murmur at the site of constriction of a branch of the pulmonary artery fully confirms the clinical impression that the murmurs observed in 2 of our patients were due to the stenosis of the pulmonary artery.

The fact that stenosis of the left branch of the pulmonary artery may produce a murmur indistinguishable in quality and location from that of a typical case of patent ductus arteriosus is of a considerable practical importance. This has been dramatically demonstrated in our case 2, in whom a thoracotomy was performed under the mistaken diagnosis of patent ductus arteriosus. Presently, surgical treatment of patent ductus arteriosus has reached such a degree of safety that in most quarters all cases are being operated on regardless of whether or not the lesions are dynamically significant. Furthermore, the presence of a typical continuous murmur is usually considered pathognomonic for this lesion, so that few cases undergo special procedures to confirm the diagnosis. The possibility of other conditions causing continuous murmurs over the thorax

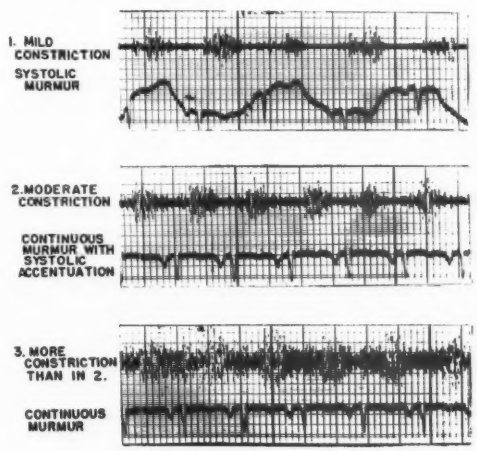


FIG. 5. Phonocardiographic record of murmurs produced during experimental constriction of dog pulmonary artery.

should constantly be kept in mind. A review of such lesions has been recently published by Davis and associates.[25] To the list of such conditions should now be added stenosis of a main branch of the pulmonary artery.

Summary

Three patients, all with other congenital cardiac malformations, were shown by cardiac catheterization to have stenosis of a main branch of the pulmonary artery. Two of the 3 patients exhibited continuous ductus-like murmurs heard at the chest wall over the site of the stenosis. The origin of the murmur at the site of the constriction was proved by the demonstration of pressure gradients throughout the cardiac cycle at the site of constriction and by the experimental production of continuous murmurs in dogs in which partial constriction of a pulmonary arterial branch was accomplished. Conditions necessary for the production of such murmurs are discussed. The importance of these observations in the differential diagnosis of congenital heart disease is emphasized and demonstrated by the fact that one of the patients underwent thoracotomy under the mistaken diagnosis of patent ductus arteriosus.

Summario in Interlingua

In tres patientes, catheterisation cardiac serviva a monstrar le presentia de un stenosis del branca major del arteria pulmonar. In omnes altere congenite malformationes cardiac esseva presente. Duo del tres patientes exhibiva continue murmures, simile al murmure de patente ducto arteriose, al pariete thoracic supra le sito del stenosis. Le origine del murmure al sito del constriction esseva provate per le demonstration de gradientes de pression durante le integre cyclo cardiac al sito del constriction e per le production experimental de continue murmures in canes in que constriction partial del branca pulmonoarterial habeva essite effectuate. Es discutite le conditiones necessari pro le production de tal murmures.

Es sublineate le importantia de iste observationes in le diagnose differential de congenite morbo cardiac. Un illustration multo significative se vide in le facto que un del patientes hic reportate esseva subjicite a thoracotomia in consequentia del diagnose erronee de patente ducto arteriose.

Addendum

Since this paper was submitted for publication, 2 additional patients with stenosis of a branch of the pulmonary artery have been studied in this laboratory.

Case 4. A 4-year-old girl without symptoms in whom a heart murmur had first been heard at the age of 9 months. Positive physical findings included a prominent apex impulse, a loud high-pitched apical systolic murmur, and in the aortic area a systolic murmur of lower frequency, which was well transmitted to the neck.

The electrocardiogram showed high voltage complexes over V_4 to V_6 and was thought to be suggestive of left ventricular hypertrophy. X-rays were interpreted as showing moderate left ventricular enlargement, slight right ventricular enlargement, and prominent proximal pulmonary arteries.

Cardiac catheterization revealed no intracardiac shunts. The arterial oxygen saturation was normal. Pulmonary artery pressure tracings, however, revealed a sharp pressure drop in the right pulmonary artery distal to the bifurcation of the main pulmonary artery. The following measurements were obtained: right ventricle 38/0 mm. Hg; main pulmonary artery 36/16 mm. Hg; left pulmonary artery 34/15 mm. Hg; right pulmonary artery 24/14 mm. Hg. Analysis of the pressure tracings revealed a gradient only during systole.

The diagnosis was aortic stenosis plus stenosis of the right pulmonary artery.

Case 5. A 5½-year-old girl without symptoms in whom a cardiac murmur was noted at the age of 2 weeks. There was a slight left parasternal lift. A thrill was noted in the left second and third intercostal spaces parasternally. A moderately loud holosystolic murmur was heard in the same area. In addition a louder systolic ejection murmur was heard in the midsternal line at the level of the second intercostal space. This murmur began after the first sound, reached its peak intensity just before midsystole and decreased in intensity during late systole.

The electrocardiogram was normal. Cardiac catheterization revealed a rise of 1.0 ml. per 100 ml. in oxygen content in the right ventricle, indicating the presence of an interventricular septal defect. There were sharp pressure drops in both right and left pulmonary arteries at their juncture with the main pulmonary artery. The pressures were: right ventricle 28/1 mm. Hg; main pulmonary artery 28/8 mm. Hg; left pulmonary artery 19/8 mm. Hg; right pulmonary artery 20/7 mm. Hg. Analysis of the pressure tracings again revealed pressure gradients only in systole. The maximum gradient on the

right side occurred 0.18 to 0.22 second after the QRS complex. This corresponded very closely in time to the point of maximum intensity of the murmur recorded phonocardiographically over the midline at the level of the second intercostal space.

This is the only patient of this series who exhibited bilateral stenosis of the pulmonary artery branches.

Comment. Several additional reports of this condition have come to our attention. Powell and Hiller[26] described a 5-year-old child in whom were found pressure gradients between the main pulmonary artery and its branches, as well as angiographic evidence of stenosis of both branches at the bifurcation of the main pulmonary artery. This patient exhibited a continuous murmur in the pulmonic area. Hodges[27] discussed the catheterization findings of a patient who had low pressures in both pulmonary artery branches in addition to a pulmonic valve stenosis. Coles and Walker[28] report a child, 26 months old, in whom angiography demonstrated a narrowing of the initial portion of each pulmonary artery branch, and in whom cardiac catheterization gave evidence of pulmonary branch stenosis as well as pulmonary valve stenosis. Figley[29] reported a patient with stenosis of the pulmonary artery branches at 3 sites. These were shown by angiography and pressure gradients were found at cardiac catheterization.

Nineteen additional cases have been studied but not reported by 4 other workers, T. Schnabel, B. Jonsson, A. Leatham, and M. Figley. In several of these other cardiac malformations were also present. Three of these cases exhibited continuous murmurs.

It becomes apparent from the number of patients discovered by these few investigators over a fairly short period of time that stenosis of the pulmonary branches is not a rare condition. The awareness of its existence will probably lead to many more such cases being discovered.

REFERENCES

1 Bredt, H.: Die Missbildungen des menschlichen Herzens. Ergebn. d. alg. Path. u. path. Anat. **30:** 77, 1936.

2 Mönckeberg, G.: Henke-Lubarsch: Handbuch der Spez path. Anatomie u. Histologie, Vol. 2, Herz und Gefässe, Berlin. Julius Springer, 1924.

3 Schwalbe, E.: Morphologie der Missbildungen, Part III, Jena, Gustav Fischer, 1909, p. 426.

4 Fürst, L.: Gerhardt's Handb. d. Kinderkrankheiten, 3, II, Tuebingen, 1878, p. 583.

5 Maugar: Réc. période. Soc. de Méd. d. Paris **13:** 74, 1802.

6 Oppenheimer, E.: Partial atresia of the main branches of the pulmonary artery occurring in infancy and accompanied by calcification of the pulmonary artery and aorta. Bull. Johns Hopkins Hosp. **63:** 261, 1938.

7 Schumaker, H., and Lurie, P.: Pulmonary valvulotomy. J. Thoracic Surg. **25:** 173, 1953.

8 Søndergaard, T.: Coarctation of the pulmonary artery. Danish Med. Bull. **1:** 46, 1954.

9 Kjellberg, S., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of congenital heart disease. Chicago, The Year Book Publishers, Inc., 1955.

10 Möller, T.: A case of peripheral pulmonary stenosis. Acta paediat. **42:** 390, 1953.

11 Arvidsson, H.: Paper read at the meeting of Svensk Förening För Medicinsk Radiologi. September 25, 1954.

12 —, Karnell, J., and Möller, T.: Multiple stenoses of the pulmonary arteries associated with pulmonary hypertension, diagnosed by selective angiocardiography. Acta radiol. **44:** 209, 1955.

13 Bouchard, F., and Cornu, C.: Etude des courbes de pressions ventriculaire droit et artérielle pulmonaire dan les retrécissements pulmonaires. Arch mal. coeur **47:** 417, 1954.

14 Sobin, S., Carson, M., Johnson, I., and Baker, C.: Pulmonary stenosis with intact ventricular septum: Isolated valvular stenosis and valvular stenosis associated with interatrial shunt. Am. Heart J. **48:** 416, 1954.

15 Keith, I., Rowe, R., Vlad, P., and O'Hanley, J.: Complete anomalous pulmonary venous drainage. Am. J. Med. **16:** 23, 1954.

16 Dimond, E., and Jones, T.: Pulmonary artery thrombosis simulating pulmonary valve stenosis with patent foramen ovale. Am. Heart J. **47:** 105, 1954.

17 Møller, P.: Studien über embolische und autochthone thrombose in der arteria pulmonalis. Beitr. path. Anat. **71:** 27, 1922.

18 Laufer, S., and Gray, I.: Organized thrombus occluding a main pulmonary artery: Report of two cases. New England J. Med. **254:** 893, 1956.

19 Saphir, O.: Bands and ridges in the pulmonary artery. Their relation to Ayerza's disease. Arch. Path. **14:** 10, 1932.

20 Craigie, D.: Instance of obliteration of the aorta beyond the arch illustrated by similar cases and observations. Edinburgh M. Surg. J. **56:** 427, 1841.

21 Edwards, J., Christensen, N., Clagett, T., and McDonald, J.: Pathologic considerations in coarctation of the aorta. Proc. Staff Meet., Mayo Clinic **28:** 324, 1948.

22 Selzer, A., Lee, R., Goggans, W., and Gerbode, F.: The effect of ouabain upon the maximum performance of the normal dog's heart. Stanford M. Bull. **11:** 253, 1953.

23 Myers, J., Murdaugh, H., McIntosh, H., and Blaisdell, R.: Observations on continuous murmurs over partially obstructed arteries. Arch. Int. Med. **97:** 726, 1956.

24 Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F.: The syndrome of patent

ductus arteriosus with pulmonary hypertension. Circulation **8:** 15, 1953.

[25] Davis, C., Jr., Dillon, R., Fell, E., and Gasul, B.: Anomalous coronary artery simulating patent ductus arteriosus. J. A. M. A. **160:** 1047, 1956.

[26] Powell, M., and Hiller, H.: Pulmonary coarctation. M. J. Australia **1:** 272, 1955.

[27] Hodges, F.: Presented at Panel Discussion on Cardiovascular Diseases. Meeting of American Medical Association, Atlantic City, New Jersey, June 8, 1955.

[28] Coles, J., and Walker, W.: Coarctation of the Pulmonary Artery. Am. Heart J. **52:** 469, 1956.

[29] Figley, M.: The expanding scope of cardiovascular radiology. Am. J. Roentgenol. **76:** 721, 1956.

Campbell, M., and Baylis, J. H.: The Course and Prognosis of Coarctation of the Aorta. Brit. Heart J. **18:** 475 (Oct.), 1956.

This paper attempts to determine the course and prognosis of coarctation of the aorta, based upon a study of 130 patients. Sixty per cent were first seen when under 20 years and only 14 per cent when over 30. Eighty patients have been followed 5 years or more. Twenty-eight were seen in the first decade. Three patients died, 1 with recurrent bouts of failure, 1 of aortic stenosis and rheumatic heart disease, and 1 of failure after being cured of bacterial endocarditis. The living patients were regarded as normal by their parents. Fifty were seen in the second decade. One died, probably of heart failure. The clinical course was usually uneventful in this decade although the blood pressure rose slowly. Thirty-seven were seen in the third decade. The blood pressure was now stabile. Five died, 1 of ruptured aorta, 1 of cerebral hemorrhage, and 3 of congestive failure. Seventeen were seen in the fourth decade. Two died, 1 with aortic regurgitation and 1 with aortic stenosis. Only a few were seen in the fifth and sixth decades.

About 25 per cent had aortic regurgitation and 5 per cent aortic stenosis. Large hearts and electrocardiographic evidence of left ventricular strain were uncommon in the absence of valvular disease. Congestive heart failure was the commonest cause of death. Below the age of 30, death was more commonly due to aortic rupture, bacterial endocarditis (with or without aortitis), and intracranial hemorrhage.

Because of the possibility of sudden and unexpected death, operation was advised for most children. Aortic regurgitation was an added reason for urging operation.

Soloff

Vasodepressor Syncope

Factors Influencing Cardiac Output

By A. M. Weissler, M.D., J. V. Warren, M.D., E. H. Estes, Jr., M.D., H. D. McIntosh, M.D., and J. J. Leonard, M.D.

Vasodepressor syncope is characterized hemodynamically by a sudden fall in total peripheral resistance with little associated change in cardiac output. The failure of the cardiac output to compensate for the fall in peripheral resistance is a striking feature of the fainting reaction. Possible explanations for this phenomenon are the presence of neurogenic myocardial inhibition or markedly limited volume of blood available to the heart. The effects of atropine injections, inflation of antigravity suit, negative pressure breathing, and albumin infusions on the syncopal reaction were studied. Results favor the causative role of limited venous inflow in the cardiac output response.

VASODEPRESSOR syncope offers an interesting experimental situation for the study of the physiologic mechanisms controlling blood pressure and cardiac output. Heretofore, only a relatively small number of observations on the cardiac output during the acute hypotensive phase have been reported.[1, 2] The difficulties in producing syncope at will, coupled with technical complications in measurement of cardiac output under such unstable circumstances, have made experiments difficult. The dye-injection method of determining cardiac output has enabled us to study not only the syncopal episode itself, but the effect of modifying experimental situations. These observations, obtained during the course of an over-all assessment of vasodepressor syncope, are the subject of the present report.

Method

The subjects were all university students. Syncope was induced by passively tilting to a 60° head-up position. Spontaneous syncope occurred in 20 per cent of the subjects. Of the remaining subjects, syncope was induced in 80 per cent by the oral administration of sodium nitrite 10 to 15 minutes prior to tilting. The entire procedure was explained to the subjects and precautions were taken to allay anxiety. Preliminary practice tilts were made in all cases to acquaint the subjects with the procedure, and to detect those who faint spontaneously.

The cardiac output was determined by the dye method of Hamilton,[3] as modified by Doyle and colleagues.[4] T-1824 in 0.5 per cent solution was injected into the central circulation through a catheter introduced into the superior vena cava or subclavian vein. The position of the catheter was determined by fluoroscopy. Arterial blood was collected in siliconized tubes from femoral or brachial arteries at 2-second intervals, and the undiluted dyed serum was promptly read on a Beckman model DU spectrophotometer. Calculations of cardiac output were made from concentration-time plots of the serum samples on semilogarithmic paper. The dye curves were scrutinized closely. Only those determinations demonstrating good delineation of the dye curves and the point of recirculation were included in the study.

Arterial blood pressures were obtained by Statham strain-gage, or Sanborn electromanometer, and recorded on direct writing or photographic multichannel recording systems.

All cardiac output data are referred to body area, and are expressed as liters per minute per square meter of body surface. Mean arterial pressures were calculated by addition of one third of the pulse pressure to the diastolic levels. Because of the slow moving camera speed utilized for prolonged observations, planimetric integration was not feasible. Total peripheral resistance (PR) was calculated from the formula $PR = (BAm \times 1332/CO)$, where BAm = mean brachial artery pressure, 1332 = conversion factor to dyne/cm.^{2}, CO = cardiac output in ml. per second. The "pulmonary blood volume" was calculated according to the Hamilton formula.[4]

A single balloon half-body antigravity suit* of the type reported by Beckman and co-workers[5] was employed in the studies of the effects of body com-

From the Department of Medicine, Duke University School of Medicine, and the Veterans Administration Hospital, Durham, N. C.

This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF18(600)1542, and in part by the American Heart Association, and by a research grant (H-1217) and a Traineeship (Dr. Leonard) from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.

* Manufactured by the David Clark Company, Worcester, Mass.

pression. With this apparatus, inflation to 60 ± 5 mm. Hg of body pressure was achieved within 10 seconds (1 pound per square inch of body pressure = 51.7 mm. Hg). Dye injections for cardiac output were made 5 seconds after initiation of suit inflation.

The carbon dioxide content of whole blood was determined by the method of Van Slyke and Neill.[6] The data were analyzed statistically according to methods outlined by Snedecor.[7]

Results

Syncope was observed in 40 subjects. The clinical picture during the course of the reaction was similar in all subjects and consisted of vague epigastric distress, nausea, pallor, sweating, mydriasis, yawning, sighing, belching, and hyperventilation followed by impaired consciousness, visual blurring, and finally unconsciousness. At times, clonic head and neck movements were in evidence. The presence of anxiety or apprehension during the syncopal reaction was unusual.

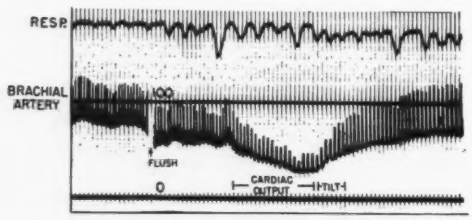


Fig. 1. Vasodepressor syncope with recovery following return to recumbency (marked "tilt"), demonstrating hypotension, bradycardia, Traube waves, and hyperventilation. Recording system was flushed at the point indicated on the illustration.

The typical arterial pressure and pneumographic changes in vasodepressor syncope are illustrated in the record of subject LB in figure 1. Of particular interest in the arterial pressure tracings are the prominent Traube-Hering waves, the forward migration and diminution in size of the dicrotic notch, and the progressive fall in systolic, diastolic, and mean arterial pressure. The hyperventilation and relative bradycardia are additional features of the reaction.

Cardiac Output During Vasodepressor Syncope

In 8 subjects cardiac outputs were determined at 60° head-up tilt before and during the syncopal reaction. Control outputs were determined 3 to 10 minutes after tilting, when the subjects were relaxed with stable blood pressure and pulse. Since presyncopal changes, e.g., yawning, nausea, pallor, sweating, mydriasis, and hyperventilation, occur at varying and unpredictable intervals before the hypotension and bradycardia, dye injections for the syncopal cardiac outputs were made only after the latter findings were in evidence on monitored records. With the onset of convulsive movements in any subject, the tilt was terminated immediately. In 7 of these subjects undamped pressure recordings at the time of the syncopal reaction revealed systolic arterial

Table 1.—*Hemodynamic Changes in Vasodepressor Syncope*

Subject	Cardiac index (L./min./M.²)			Mean arterial pressure (mm. Hg)			Peripheral resistance (Dyne-sec./cm.⁵)		
	Control	Syncope	Change	Control	Syncope	Change	Control	Syncope	Change
GH	3.5	2.2	−1.3	100	38	−62	1128	689	−439
BW	2.5	1.6	−0.9	74	30	−44	1302	812	−490
BJ	3.2	2.5	−0.7	85	26	−59	1125	426	−699
DF	2.9	2.3	−0.6	80			1108		
LD	2.4	1.9	−0.5	82	55	−27	1407	1226	−181
JF	2.7	2.5	−0.2	87	57	−30	1358	956	−402
MS	2.2	2.5	+0.3	67	27	−40	1132	392	−740
LB	3.8	4.3	+0.5	95	32	−63	1064	320	−744
Mean	2.9	2.5	−0.4	84	38	−46	1217	689	−528
Sd*			0.21						80
p			> .05						< .01

All data obtained while the subjects were in the 60° head-up tilt position.
* Refers to standard error of the difference between means.

pressure levels ranging from 84 mm. to 33 mm. Hg, and diastolic levels of 54 mm. to 24 mm. Hg, with a mean of 54/33 for the group. The mean arterial pressure data are recorded in table 1.

The cardiac outputs observed in the 8 subjects in this series are summarized in table 1. Subjects DF and LB received no nitrite. Although the mean fall in cardiac index of 0.4 L. is not statistically significant, the data indicate a tendency for the cardiac output to fall slightly during syncope. In 3 additional subjects in whom control tilted outputs for comparison were not obtained, the cardiac indices during fainting were 2.6, 2.6, and 2.4 L. respectively. The mean resting cardiac index at 60° head-up tilt in a group of 30 subjects in this laboratory is 2.7 L. (S.D. ± 0.3).

Stroke volume changes were variable and revealed no consistent trends. During syncope a relative bradycardia is always observed when the pulse rate is compared to the usual presyncopal tachycardia.

As expected from the above data, decreases in peripheral resistance occurred in all of the subjects (table 1). The mean change from 1217 to 689 units is significant ($p < .01$). Two additional subjects, in whom peripheral resistance in the tilted position before fainting could not be calculated, demonstrated falls of 924 and 620 units respectively when compared to their peripheral resistance in the recumbent position.

TABLE 2.—*"Pulmonary Blood Volume" in Vasodepressor Syncope*

Subject	Control (ml.)	Syncope
GH	2336	1423
BW	1067	821
BJ	1601	1236
DF	1952	1356
LD	1662	1560
JF	1365	1301
MS	1679	1778
LB	1794	1385
Mean	1682	1358
Sd*	115	
p	$< .05$	

All data obtained while subjects were in the 60° head-up tilt position.

* Refers to standard error of the difference between means.

The estimated "pulmonary blood volume" was calculated in the 8 subjects in this series. The results are tabulated in table 2, and demonstrate a close correlation with the cardiac output changes. The mean circulation time during syncope averaged 18.0 seconds, which is not significantly different from the control average of 17.6 seconds.

Cardiac Index During Recovery from Syncope Following Resumption of Recumbency

Upon resumption of the recumbent posture in the course of vasodepressor syncope, there is prompt reversal of the blood pressure and pulse changes, and recovery of consciousness (fig. 1). On 2 occasions inordinately elevated cardiac indices were registered when dye output determinations were made immediately after return to the horizontal position. In order to investigate this phenomenon further, 5 additional studies were obtained in which syncope was induced in the usual manner and output determinations were made immediately after reverse tilt. To accomplish this, the dye was injected during the course of the reverse tilt. The data are summarized in table 3. A mean cardiac index rise of 2.4 (S.E. ±0.9)* L. per minute per $M.^2$ above resting recumbent levels was observed during the first 30 seconds following return to the horizontal position. In all of the above subjects complete recovery, save persistent pallor and occasional headache, occurred within 45 seconds of the reverse tilt, so that the cardiac output rise occurred during the period of recovery. When compared to the cardiac index during syncope (table 1), the rise in cardiac index following return to recumbency is highly significant ($p < .01$). Of additional interest in all subjects following the reverse tilt was a transient but marked flush and tachycardia, each lasting no longer than 15 seconds.

Effects of Inflation of Antigravity Suit

In an attempt to assess the role of diminished venous inflow to the heart in the hemodynamic

* Refers to standard error of the mean.

TABLE 3.—*Cardiac Index during Recovery from Vasodepressor Syncope Following Resumption of Recumbency*

Subject	Before syncope (L./min./M.²)	During recovery
RT	2.9	9.9
DT	2.5	5.0
DL	3.4	4.0
RH	3.7	3.8
RK	2.8	6.4
AW	3.4	5.0
FA	2.7	4.0
Mean	3.1	5.4

All of the above determinations were performed while the subjects were in the horizontal position.

TABLE 4.—*Cardiac Index in Normal Subjects after Antigravity Suit Inflation*

Subject	Before inflation (L./min./M.²)	After inflation*
RN	1.8	2.4
HY	2.3	3.7
RK	2.8	2.5
JM	2.7	3.8
ST	2.3	3.0
MM	2.6	3.6
CH	3.1	3.0
TP	2.1	2.2
TH	2.2	3.5
RD	2.3	2.4
JG	1.8	2.7
Mean	2.4	3.0
Sd†	0.18	
p	<.01	

All data obtained while subjects were in the 60° head-up tilt position.

* Data obtained during the first 30 seconds following inflation to 60 ± 5 mm. Hg body pressure.

† Refers to standard error of the difference between means.

picture of vasodepressor syncope, the effects of application of external pressure in the normal and syncopal state were studied.

Inflation of the antigravity suit to 60 ± 5 mm. Hg body pressure in the standing position is attended by little or no discomfort to the subject. Because of the alarm of sudden inflation and the tendency of the subject to tense the abdominal muscles, practice inflations had been carried out before the actual studies were

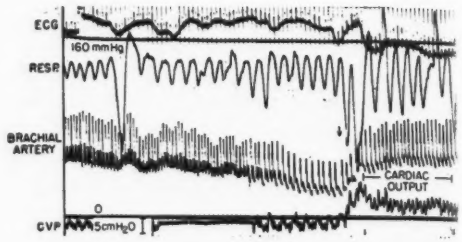


FIG. 2. Vasodepressor syncope with recovery following antigravity suit inflation. Arrow indicates point of inflation. CVP represents central venous pressure.

initiated. In the normal subject at 60° head-up tilt, antigravity suit inflation results in a prompt increase in pulse pressure (5–10 mm.), predominantly a result of elevated systolic pressure and a moderate slowing of the pulse. In table 4 are summarized the cardiac output data in 11 subjects in whom determinations were made with subjects at 60° head-up tilt before and after antigravity suit inflation. The mean increase of 0.6 L. per minute per M.² following antigravity suit inflation, representing a 25 per cent elevation above the control output for the group, is significant ($p < .01$). Peripheral resistance following antigravity suit inflation tends to fall slightly, averaging 206 units below control levels ($p = 0.1$).

Inflation of the antigravity suit in the course of a syncopal reaction is attended by dramatic recovery of consciousness and resolution of symptoms within 30 seconds. The typical hemodynamic response to inflation during syncope is illustrated in figure 2. In the left side of the figure, the usual pressure, pulse, and respiratory changes of vasodepressor syncope are seen. Of additional interest in this illustration is the central venous pressure, which remained unaltered throughout the course of the syncopal reaction until its rise after the suit was inflated. Immediately following inflation of the antigravity suit there is a rise in systolic, diastolic, and mean arterial pressure, and disappearance of the relative bradycardia.

A summary of the effects of antigravity suit inflation on the cardiac output in the course of syncope appears in table 5. In each of the subjects, the determination of cardiac output

followed immediately (5 seconds) after inflation of the antigravity suit and coincided with the improvement in the course of the syncope. Comparison with table 4 demonstrates the slightly more marked effect of antigravity suit inflation in syncope as compared to the normal standing posture. When compared to the cardiac index during syncope (table 1), the rise in cardiac index following antigravity suit inflation during syncope is significant ($p < .05$).

The mean peripheral resistance following antigravity suit inflation during syncope in 7 of the above subjects (819 units S.E. 96) was not significantly different from the mean peripheral resistance during unaltered syncope, despite the fact that the syncopal changes were reversed at the time of the postinflation determinations.

In summary, antigravity suit inflation in the normal subject at 60° head-up tilt is accompanied by an increase in cardiac output and slight fall in peripheral resistance. In vasodepressor syncope, the prompt improvement after antigravity suit inflation is associated with an increased cardiac output and little or no change in peripheral resistance.

Effects of Negative Pressure Breathing and Albumin Infusions

Full-phase negative-pressure breathing (minus 16 to minus 19 mm. Hg) was maintained by having the subjects breathe from a counterweighted Tissot apparatus. A face mask was secured in place before the experimental tilt, and by a stopcock device the subjects could be maintained on atmospheric pressure until the maximum hypotension was reached. The apparatus was filled with 50 per cent oxygen in air. Carbon dioxide accumulation was prevented by allowing expired air to pass through a potassium hydroxide chamber before reentering the negative-pressure chamber. In 3 subjects prompt recovery and reversal of the hypotension was noted when negative pressure was applied at the height of syncope, despite the fact that the subjects were maintained in the upright position.

In 3 additional subjects, all of whom experienced previous syncope, induction of syncope was attempted by the usual nitrite and tilt procedure immediately following completion of a rapid infusion (20 minutes) of 1000 ml. of 5 per cent albumin in saline. In none of the individuals was a syncopal or presyncopal change noted, despite the fact that each was maintained at 60° tilt for 30 minutes following nitrite administration. In 2 of these subjects syncope was subsequently induced by the tilt-nitrite procedure.

Effect of Atropine

In 5 individuals 1.6 to 2.4 mg. of atropine were injected into the central circulation via the venous catheter 2 to 5 minutes prior to the onset of syncope induced by the tilt-nitrite procedure. Dramatic hastening of the pulse indicative of vagal blockade occurred in each case. Syncope progressed in the usual manner, despite the absence of bradycardia. Cardiac output determinations at the time of syncope in these subjects revealed a mean cardiac index of 2.5 L. per minute per $M.^2$ (S.E. ± 0.1), and demonstrated no significant deviation from the cardiac index during syncope in the nonatropinized subjects.

Arterial Carbon Dioxide

In 10 subjects arterial carbon dioxide content was determined in the 60° head-up tilt position 1 to 3 minutes before, and again, at the height of syncope. The results revealed a uniform fall

TABLE 5.—*Cardiac Index in Vasodepressor Syncope after Antigravity Suit Inflation*

Subject	Before syncope (L./min./$M.^2$)	Syncope and inflation*
RN	1.8	2.9
RK	2.8	4.2
LD	2.4	3.1
JM	2.7	4.4
CH	3.1	3.8
TP	2.1	2.2
TH	2.2	3.9
RD	2.3	2.5
Mean.....	2.4	3.4

All data obtained while subjects were in the 60° head-up tilt position.

* Data obtained during the first 30 seconds following inflation to 60 ± 5 mm. Hg body pressure during the syncopal reaction.

TABLE 6.—*Arterial Carbon Dioxide Content in Vasodepressor Syncope*

Subject	Before syncope* (Vol.%)	During syncope† (Vol.%)
JC	48.8	45.3
JH	45.8	41.7
JT	44.7	42.7
TP	43.1	39.2
DR	50.9	44.7
RF	47.8	37.2
CL	42.4	36.8
JL	46.9	43.1
DS	46.7	45.5
GW	46.4	43.4
Mean	46.4	42.0
Sd‡	0.83	
p	$<.01$	

All samples obtained while subjects were in the 60° head-up tilt position.

* Samples drawn within 3 minutes before onset of syncopal changes.

† Samples drawn at the time of maximum hypotension.

‡ Refers to standard error of the difference between means.

averaging 4.4 volumes per cent ($p < .01$) (table 6).

DISCUSSION

In the normal individual the arterial blood pressure is maintained within narrow limits by a balance between the cardiac output and the effective peripheral resistance. In the event of a fall in peripheral resistance, the arterial pressure is maintained by an increased cardiac output. This response of the cardiac output to a sudden fall in peripheral resistance has been well demonstrated in individuals with large areas of reactive hyperemia,[8] and in patients with arteriovenous fistula.[9] A striking feature of the observations on vasodepressor syncope reported here is the failure of the cardiac output to rise in the face of a decreased peripheral resistance. It is upon the nature of this apparent dissociation of the cardiac output and peripheral resistance responses that our interest is centered in the present study.

The absence of a compensatory rise in cardiac output in the presence of a diminished peripheral resistance may be explained by reflex myocardial inhibition or marked limitation on the volume of blood available to the heart. The observations on the effect of return to recumbency demonstrate that the cardiac output often increases above resting levels during the recovery process, indicating a removal of those factors responsible for the restriction of the cardiac output. Since the rise in cardiac output during the termination of a syncopal reaction could be accomplished by removal of either or both of the aforementioned mechanisms restricting cardiac output, it was necessary to evaluate the relative significance of each factor individually by studying the cardiac output responses under various experimental conditions while the subjects were maintained in the tilted posture.

Observations on the existence of myocardial vagal inhibition[10] suggested that a vago-inhibitory effect might explain the cardiac output response during syncope. In addition, slowing of the heart, long recognized as occurring during syncope, might of itself be a restrictive factor on the heart's ability to compensate. The effect of atropine on the cardiac output response in syncope was therefore studied. Despite the presence of marked tachycardia and apparent vagal blockade at the height of syncope, the cardiac output response to the fall in peripheral resistance was no different from that in the nonatropinized subjects. The factor of bradycardia therefore does not appear to be the limiting one in restricting the cardiac output. In addition, atropine-sensitive cardio-inhibition probably does not play a significant role in the cardiac output response in syncope.

Attention was next directed to the second possible mechanism of cardiac output restriction. The effects of increasing the volume of blood available to the heart by antigravity suit inflation, negative-pressure breathing, and albumin infusion were studied. Each of these factors was found either to abort or to prevent the hypotensive phase of syncope. Because of the ease of experimental control and the efficacy of its action, the antigravity suit was studied most extensively. Inflation of the antigravity suit resulted in termination of the hypotension and simultaneous elevation of the cardiac output. These changes occurred despite the fact that the subjects were maintained in the upright position, and strongly suggest that

the factor of limited venous inflow plays a significant role in the restriction of the cardiac output in syncope. Although the data concerning the effects of situations designed to enhance venous inflow to the heart do not eliminate the possibility of concomitant neurogenic myocardial inhibition, it appears unnecessary to invoke the latter factor as an additional explanation for the diminished cardiac output response in syncope.

The fall in arterial carbon dioxide content is probably secondary to the hyperventilation during syncope. Hypocapnia secondary to hyperventilation has been demonstrated to result in mild to moderate hypotension, increased forearm blood flow, and diminished cerebral blood flow.[11, 12] Despite these changes, all of which are well known components of the circulatory picture of vasodepressor syncope, acute hyperventilation alone uncommonly produces typical vasodepressor syncope. It is thought therefore that the hypocapnia during syncope is an important factor in accentuating the circulatory embarrassment, but probably is not an essential component of the reaction. Supporting this view is the finding that inhalation of 5 per cent carbon dioxide tends to diminish or eliminate the hypocapnia without otherwise altering the syncopal reaction.[13]

The observed fall in total peripheral resistance in our subjects is of interest in light of studies on specific vascular beds. Although blood flow effects have varied, the syncopal reaction has been found to result in a decreased vascular resistance in the muscle,[14] splanchnic,[15] and renal[16] circulations.

Engel and Romano[17] have suggested that fainting represents an incomplete response in the preparation for flight occurring in situations where muscular activity is repressed. The physiologic adaptations for motion are thus incomplete, with resultant circulatory disorganization. The findings reported in this paper are consistent with this thesis.

From a circulatory standpoint, therefore, fainting might be characterized by a series of events initiated by a precipitous fall in peripheral resistance and arterial blood pressure occurring in the face of a situation where the heart does not compensate by increased output. Although the present study has focused attention on these circulatory aspects of syncope, it is clear that other facets, such as emotional and humoral factors, are involved.

Summary

Postural syncope can be produced with facility by 60° head-up tilt with the aid of sodium nitrite. Syncope so induced is similar to spontaneous vasodepressor syncope, and offers an experimantal technic for the study of regulation of blood pressure and cardiac output.

The cardiac output in vasodepressor syncope tends to fall slightly. During recovery, the cardiac output rises at times to supernormal levels. Of particular interest is the failure of the cardiac output to compensate for the fall in peripheral resistance during syncope. The occurrence of either neurogenic myocardial inhibition or markedly limited venous inflow were investigated as possible explanations for this finding.

Atropinization prevents the relative bradycardia during syncope, but does not alter the cardiac output response.

Antigravity suit inflation or negative-pressure breathing rapidly reverses the syncopal reaction. The improvement following antigravity suit inflation is associated with a rise in cardiac output and insignificant changes in peripheral resistance. Albumin infusions were found to prevent syncope.

The arterial carbon dioxide content falls at the height of syncope. This fall is probably secondary to the hyperventilation during syncope, and contributes to the circulatory embarrassment by further lowering peripheral resistance and cerebral blood flow.

The major circulatory event of vasodepressor syncope would appear to be not only widespread loss of peripheral resistance, but its occurrence in the face of inability of the heart to compensate by an increase in output. Present evidence favors the causative role of limited inflow in restricting the response of cardiac output.

Summario in Interlingua

Syncope postural es facile a producer per basculation a 60° (capite in alto) con le adjuta de nitrito de natrium. Le syncope assi inducite es simile al spontanee syncope vasodepressori e

representa un technica experimental pro le studio del regulation de pression sanguinee e rendimento cardiac.

In syncope vasodepressori le rendimento cardiac tende a reducer se levemente. Durante le recovramento le rendimento cardiac cresce a vices usque a nivellos supranormal. De interesse special es le facto que le rendimento cardiac non compensa le reducite resistentia peripheric que occurre durante le syncope. Esseva investigate, como explicationes possibile de ille phenomeno, le occurrentia de neurogene inhibition myocardial o de un marcate limitation del influxo venose.

Atropinisation preveni le bradycardia relative durante le syncope, sed illo non altera le responsa del rendimento cardiac.

Le pression exercite per le inflation de un costume de gravitate o le effectuation de respiration a pression negative reverte le reaction syncopic rapidemente. Le melioration que occurre post le inflation del costume de gravitate es associate con un augmento del rendimento cardiac e non-significative alterationes del resistentia peripheric. Esseva trovate que infusiones de albumina preveni le syncope.

Le contento arterial de bioxydo de carbon se reduce al culmine del syncope. Iste reduction es probabilemente secundari al hyperventilation durante le syncope e contribue al disturbation circulatori per causar un reduction additional del resistentia peripheric e del fluxo de sanguine cerebral.

Le major evento circulatori in syncope vasodepressori es apparentemente non solo le perdita extense de resistentia peripheric sed le occurrentia de iste perdita in association con le incapacitate del corde de effectuar un compensation per augmentar su rendimento. Le datos nunc disponibile pare attribuer un rolo causative al reducite influxo in le restriction del responsa del rendimento cardiac.

REFERENCES

[1] Barcroft, H., Edholm, O. G., McMichael, J., and Sharpey-Schafer, E. P.: Posthemorrhagic fainting: Study by cardiac output and forearm flow. Lancet **1:** 489, 1944.

[2] Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J.: Effect of venesection and pooling of blood in extremities on atrial pressure and cardiac output in normal subjects, with observations on acute circulatory collapse in 3 instances. J. Clin. Invest. **24:** 337, 1945.

[3] Hamilton, W. P.,, Moore J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. **99:** 534, 1932.

[4] Doyle, J. T., Wilson, J. S., Lepine, C., and Warren, J. V.: An evaluation of the measurement of the cardiac output, and the so-called pulmonary blood volume, by the dye-dilution method. J. Lab. Clin. Med. **41:** 1, 1953.

[5] Beckman, E. L., Slaughter, O. L., and Wood, E. H.: Measurements to evaluate the effectiveness of the full pressure half suit in applying external pressure to the body. Aviation Medical Accleration Laboratory, U. S. Naval Air Development Center Report No. NADC-MA-5502, 1955.

[6] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurements. I. J. Biol. Chem. **61:** 523, 1924.

[7] Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology. Ames, Iowa, Iowa State College Press, 1940.

[8] Stead, E. A., Jr., and Warren, J. V.: Cardiac output in man: An analysis of the mechanisms varying the cardiac output, based on recent clinical studies. Arch. Int. Med. **80:** 237, 1947.

[9] Nickerson, J. L., Elkin, D. C., and Warren, J. V.: The effect of temporary occlusion of arteriovenous fistulas on heart rate, stroke volume, and cardiac output. J. Clin. Invest. **30:** 215, 1951.

[10] Peterson, L. H.: Some characteristics of certain reflexes which modify the circulation in man. Circulation **2:** 351, 1950.

[11] Burnum, J. F., Hickam, J. B., and McIntosh, H. D.: The effect of hypocapnia on arterial blood pressure. Circulation **9:** 89, 1954.

[12] Kety, S. S., and Schmidt, C. F.: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, and cardiac output and blood pressure of normal young men. J. Clin. Invest. **25:** 107, 1946.

[13] Unpublished observations.

[14] Barcroft, H., and Edholm, O. G.: On vasodilatation in human skeletal muscle during posthemorrhagic fainting. J. Physiol. **104:** 161, 1945.

[15] Bearn, A. G., Billing, B. H., Edholm, O. G., and Sherlock, S.: Hepatic blood flow and carbohydrate changes in man during fainting. J. Physiol. **115:** 442, 1951.

[16] DeWardener, H. H., and McSwiney, R. R.: Renal hemodynamics in vaso-vagal fainting due to hemorrhage. Clin. Sc. **10:** 209, 1951.

[17] Engel, G. L., and Romano, J.: Studies of syncope: Biological interpretations of vasodepressor syncope. Psychosom. Med. **9:** 288, 1947.

Atrial Dissociation and Uniatrial Fibrillation

By GEORGE W. DEITZ III, M.D., HENRY J. L. MARRIOTT, M.D., EVAN FLETCHER, M.D., AND SAMUEL BELLET, M.D.

Three cases of atrial dissociation are illustrated with electrocardiograms. The coexisting atrial rhythms observed in published cases permit us to offer a convenient classification. Two possible explanations of this rare phenomenon are discussed.

ATRIAL dissociation has been repeatedly observed in the exposed heart of the experimental animal. There is no reason to believe that the phenomenon may not occur spontaneously in the human heart.

The purposes of this communication are to present tracings and to draw attention to this little-discussed phenomenon and to include examples of what we have chosen to call uniatrial fibrillation.

LITERATURE

Numerous authors have claimed to demonstrate independent rhythms in the 2 atria. Hering[1] in 1900 first recorded dissociation of the atria in the experimental animal, whereas Wenckebach[2] in 1906 was first to report it in man. Neither of these authors illustrated his claim with published electrocardiograms.

A number of these publications invite special comment. Schrumpf[3] published the first illustrative electrocardiogram; his tracing appears reasonably convincing, but Lewis,[4] quite properly setting the sceptical pace for all subsequent critics, refused to accept it and pointed out that "it is necessary to be hypercritical in dealing with exceptional curves of this kind, owing to the important conclusions which they would otherwise justify." The 3 tracings published by Bay and Adams[5] are further good examples of the double P-wave type. As an argument in favor of the reality of atrial dissociation in their cases, they pointed out that the secondary atrial waves in 2 of their records showed a phasic arrhythmia affecting the normal P waves.

Condorelli's tracing of simultaneous fibrillation and sinus rhythm[6] affords excellent experimental basis for clinical claims of uniatrial fibrillation. By ligating the left anterior atrial artery he produced atrial dissociation on 2 occasions with sinus rhythm persisting in the right atrium and controlling the ventricles, while the left atrium was fibrillating.

The tracing of Lombardini and Aviles[7] shows a remarkable, rapid and regular atrial wave at a rate of 765 per minute with superimposed normal sinus P waves at a rate of 90. There is no constant relationship between the P waves and the "micro-flutter" waves; complete A-V block is also present with an idioventricular rhythm at a rate of 23. They stated that the flutter contractions were distinctly audible on auscultation and they assumed that microflutter occupied the left atrium while sinus rhythm controlled the right.

A tracing published by Bellet[8] shows inverted P waves at a rate of 82 in lead II with a P-R interval of 0.12 second, while simultaneous atrial deflections, probably representing flutter, occurred at a rate of 300 in a simultaneous esophageal lead.

In the interesting tracing published by Moreira[9] fibrillation is evident in V_1, while P waves at a rate of about 106 are seen in other precordial leads as well as superimposed on the fibrillatory waves in V_1. Ventricular response is completely irregular, indicating that the ventricles are responding to the atrial fibrillation rather than to the sinus impulses. The tracings presented by Dagnini[10] and De Castro[11] are less convincing examples of uniatrial fibrillation.

Electrocardiograms published by other authors[12–16] and referred to in other reviews on atrial dissociation appear to represent intra-atrial block rather than atrial dissociation.

CASE REPORTS

Since strophanthin excess can produce atrial dissociation experimentally,[17] the possible role of

From the Philadelphia General Hospital, Philadelphia, Pa., and the Mercy Hospital, Baltimore, Md.

digitalis intoxication in its clinical production must be considered. For this reason, in the case histories that follow, digitalis dosage has been accorded detailed attention.

Case 1. J. McN., a 5½-month-old child, was admitted to Philadelphia General Hospital with congestive heart failure associated with a ventricular septal defect. Serial tracings confirmed the presence of digitalis intoxication, but the dosage of digitalis was uncertain. Atrial dissociation was recorded on numerous occasions by 2 different direct writing machines and 1 photographic mirror galvanometer. From approximately 100 feet of tracings representative examples were taken. Figure 1 shows a sinus arrhythmia at a rate of 83 with irregularly recurring p waves appearing before, during, or after the sinus P waves. These waves appear to initiate short bursts (0.10–0.32 second) of rapidly occurring waves (1500 per minute) of low voltage (0.01–0.05 mv.). Figure 2 at a higher magnification demonstrates the smaller waves. This illustrates repetitive short paroxysms of "uniatrial" fibrillation with sinus P waves controlling the ventricular rate. The rate of these rapid, diminutive waves is similar to that of the intermediate form of fibrillatory waves described by Prinzmetal,[18] which produce a "glass-like" baseline in the standard electrocardiogram.

Case 2. D. W., a 58-year-old Negro woman, was first seen in the Cardiac Clinic at Mercy Hospital, Baltimore, in July 1954 for congestive heart failure. Her blood pressure was 140/94, and the electrocardiogram showed left ventricular hypertrophy and strain. She was started on digitalis folia, 0.1 Gm. t.i.d. for a week and was then maintained on 0.1 Gm. daily. On August 25, 1955, she complained that she had felt her heart fluttering for the past few days. For 2 days she had taken an extra tablet of digitalis. The clinical impression was atrial fibrillation with a ventricular rate of 68 per minute; unfortunately no electrocardiogram was taken. On October 29 she had no complaints but the rhythm was described as "regular for as many as 7 beats, followed by a shower of irregular beats." An electrocardiogram taken a week later (fig. 3) showed first degree A-V block (P-R 0.22 second) and a more marked pattern of left ventricular hypertrophy and strain. On a subsequent occasion this patient was deliberately intoxicated with Digoxin, which produced incomplete A-V block with Wenckebach phenomenon, but no disturbance of the atrial rhythm.

Lead V_6 (fig. 3) shows the appearance, acceleration, and decay of excitability in an ectopic atrial focus. The first few p waves, as isolated phenomena, may be considered as nonconducted ectopic atrial beats; after a few seconds, when the rate has in-

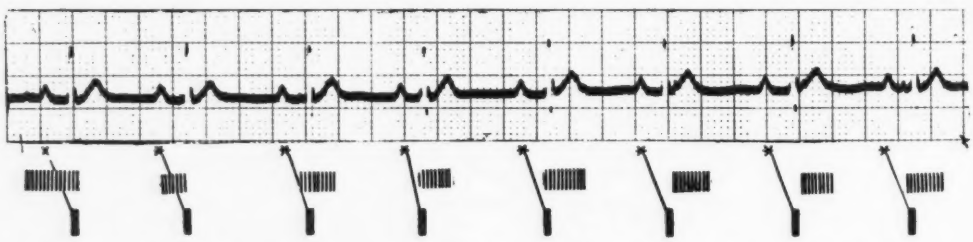


FIG. 1. Lead II. The short vertical lines represent the bursts of rapidly occurring waves of low voltage.

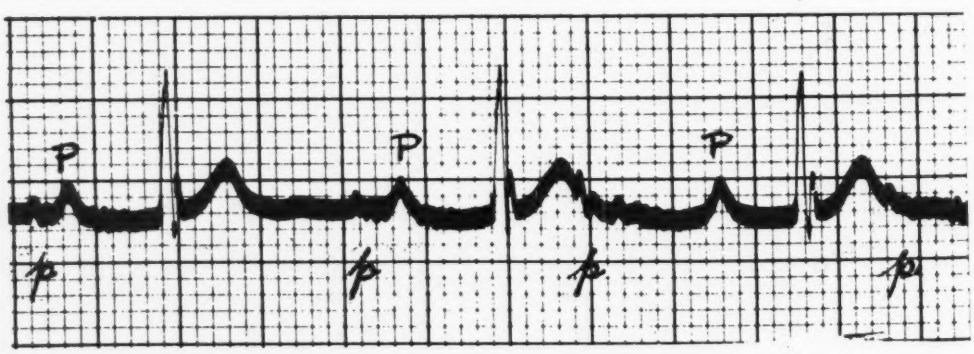


FIG. 2. Lead II. A higher magnification of a representative cutting clearly demonstrates the waves of uniatrial fibrillation (*p*). Rate, 1500 per minute; duration, 0.10 to 0.32 second; voltage, 0.01 to 0.05 mv. The sinus P waves continue undisturbed.

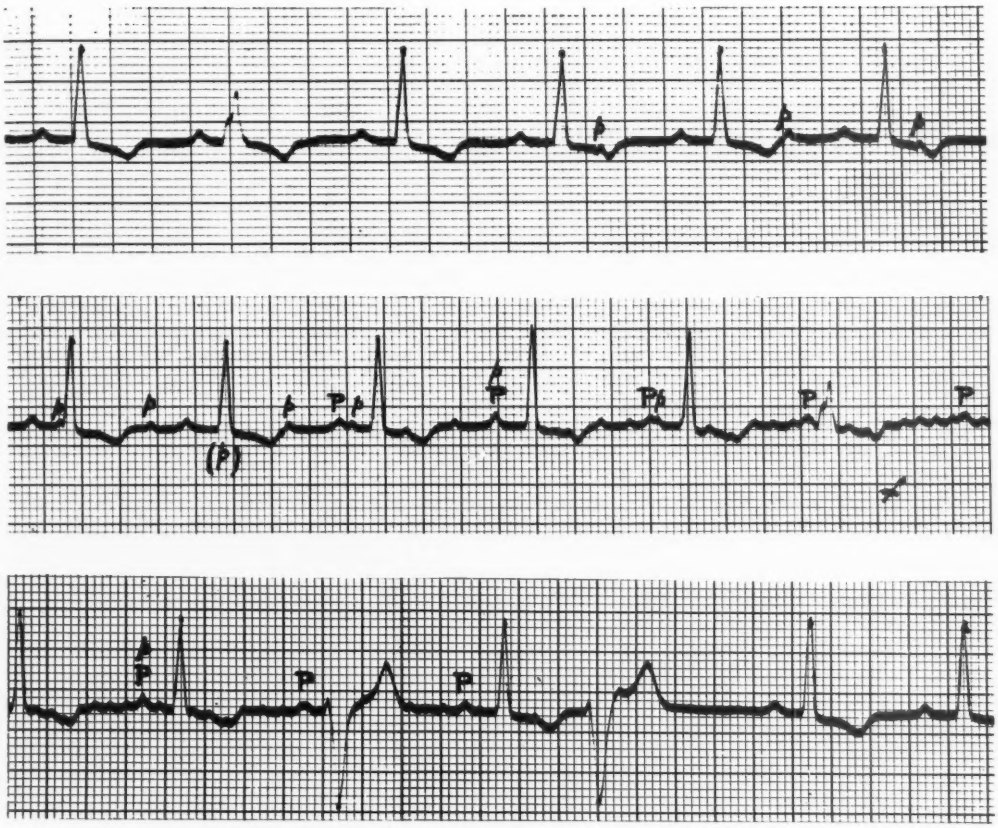


FIG. 3. Lead V_6. The 3 strips are continuous. After a few normal sinus beats secondary atrial waves (*p*) appear, at first nearly 1 second apart, but rapidly increasing in incidence until at the beginning of the bottom strip they have attained a rate of 750 per minute; they then slow and disappear quickly. Meanwhile sinus P waves continue throughout with undisturbed regularity.

creased to between 150 and 200, they may well be considered to represent atrial tachycardia; after 2 or 3 more seconds when they reached a rate of 750, their rhythm must certainly be called fibrillation or, in view of their regularity, microflutter. Thus in a few brief seconds "the unitary nature of the auricular arrhythmias," as propounded by Prinzmetal,[18] is spontaneously illustrated. Sinus P waves meanwhile continue uninterrupted and are absolutely regular.*

* The capture of this tracing emphasizes the value of training the electrocardiographic technician to observe with an intelligent eye what is being recorded. In the present instance an unusually long strip was secured because the interested technician perceived that something unusual was occurring and so continued the tracing until the phenomenon had subsided.

Case 3. M. D., a 57-year-old Negro woman was seen in the Mercy Hospital dispensary on July 9, 1953, with symptoms of congestive heart failure; her blood pressure was 178/126. She was digitalized with digitoxin and followed for a few weeks but then was not seen again for nearly 2 years. In June 1955 she returned, having taken no digitalis for 3 months. This time she was digitalized with gitaligin; she received 9 mg. in a week and lost over 11 pounds and then became anorexic. Gitaligin was reduced to 0.5 mg. daily. When next seen 2 weeks later, she was nauseated and maintenance therapy was changed to digitoxin 0.05 mg. daily until August 31. At this time she again complained of shortness of breath of 2 weeks' duration, and the dose of digitoxin was increased to 0.1 mg. daily. Eight days later an electrocardiogram showed A-V dissociation. On September 15, the heart was irregular at a rate of 60 and digitoxin was stopped for 1 week. On Sep-

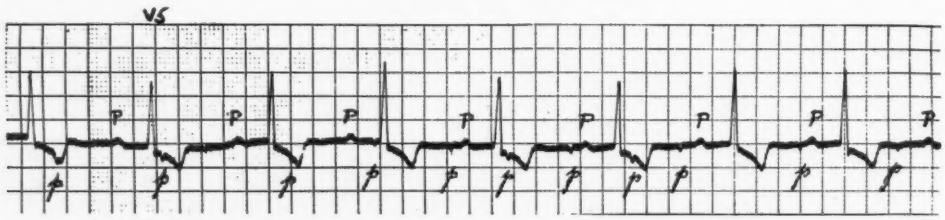


FIG. 4. Lead V_5. A secondary set of *p* waves is present independent of the sinus P waves.

tember 20 an electrocardiogram showed sinus bradycardia at a rate of 55 with partial A-V block (P-R 0.28 second). In lead V_5 a secondary set of atrial waves, independent of the P waves, was present (fig. 4). Digitalis was withheld until September 28, when another electrocardiogram showed a P-R interval of 0.20 second and occasional ventricular premature beats. Gitaligin 0.5 mg. daily was then started. Several subsequent tracings have failed to reveal any signs of atrial disturbance.

DISCUSSION

A variety of terms has been used to describe dissociation between the atria; intra-auricular,[4, 8] interauricular,[9, 12, 19] interatrial,[20] atrial[21] dissociation, and interatrial block.[20–23] There is clearly need for consistency and it would seem to us that the simplest, least ambiguous, and most acceptable term is *atrial dissociation*. Intra-atrial block refers to a distinct and different condition of abnormally widened and notched P waves, well exemplified by P-mitrale.

In previous publications dealing with atrial dissociation, various symbols have been used to designate the 2 sets of atrial waves: They have been labeled P and P′,[24–26] P′ and P″,[13] P_1 and P_2,[3] and P and p.[19] P′, however, is the accepted label for atrial waves that substitute for, rather than appear in addition to, the normal sinus P wave. P′ thus represents an atrial wave arising from an ectopic focus that controls the 2 atria if not the whole heart, as in an ectopic atrial beat or in paroxysmal atrial tachycardia. We therefore propose that the symbol p, as used by Lian and Globlin,[19] is most suitable for the secondary atrial waves that appear in parallel with existing P (or P′) waves in atrial dissociation.

When a clinical record is interpreted as atrial dissociation, critics are quick to point out that the second system of waves may be artifacts—such as interference from a dial telephone, from an electric saw or buzzer, from hiccoughs, from contact with another person whose QRS complexes are registered on a diminutive scale. Katz[27] summarized the situation as follows: "While this possibility exists, the evidence presented in the cases reported is far from convincing, since the phenomena described could readily be explained by artifacts." White,[23] more recently, has concurred: "Its occurrence in man, although suggested and described, has not been conclusively proved."

If dissociation between the atria occurs, 2 mechanisms seem possible: (1) each atrium *in toto* is separately autonomous (this has as its experimental precedent the production of atrial dissociation by interruption of interatrial pathways)[6, 14, 28] or (2) a part of 1 atrium is independent from the rest of the mass of atrial muscle, as experimental dissociation of a small part of atrial muscle has been observed in the dog's heart after intoxication with strophanthin[17] and yohimbine.[29] The second possibility presupposes that the dissociated areas of the atria must be mutually protected against each other's impulses by "entrance" and "exit" blocks. Whether the whole or only a part of 1 atrium is involved in the ectopic rhythm, it would seem appropriate to apply the term uniatrial to this pararrhythmia.

Subsequent examples of atrial dissociation, based on published electrocardiographic evidence, can be conveniently classified into 4 groups:

1. Two parallel sets of atrial waves each maintaining its own independent rhythm (a situation that the French authors picturesquely call "la double commande").[3, 5, 19, 24–26, 30, 31]

2. Flutter in one atrium, fibrillation in the other.[32–35]

3. Sinus or nodal rhythm in the right atrium, flutter in the left atrium.[7, 8]

4. Sinus or nodal rhythm in the right atrium, fibrillation in the left atrium[6, 9, 10, 11] that can be either fixed or repetitive.

Of the cases presented here, the first 2 belong in group 4 of this classification, while case 3 belongs in group 1.

Summary

The inconsistent terminology hitherto used to describe the phenomenon of dissociation between the atria is commented upon and appropriate terminology is recommended for consistent usage.

Three cases of atrial dissociation, 2 with uniatrial fibrillation, are presented and illustrated with electrocardiograms. A classification is offered based upon the coexisting atrial rhythms. Previous examples of atrial dissociation are reviewed. A paroxysmal repetitive form of uniatrial fibrillation is presented for the first time.

Summario in Interlingua

Es notate le manco de systema in le terminologia usate usque nunc in describer le phenomeno del dissociation inter le atrios. Un terminologia appropriate es recommendate in le interesse de un usage plus systematic.

Es presentate tres casos de dissociation atrial. Duo es characterisate per fibrillation uniatrial. Le casos es illustrate per electrocardiogrammas. Es proponite un classification super le base del coexistente rhythmos atrial. Previe exemplos de dissociation atrial es passate in revista. Un forma repetitive paroxysmal de fibrillation uniatrial es presentate pro le prime vice.

REFERENCES

[1] Hering, H. D.: Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages. Arch. ges. Physiol. **82:** 1, 1900.

[2] Wenckebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit. Arch. f. Anat. u. Physiol. Physiologische Abteilung, 297, 1906.

[3] Schrumpf, P.: De l'interference de deux rythmes sinusaux; preuve du dualisme du nodule de Keith. Arch. mal. coeur **13:** 168, 1920.

[4] Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, Ed. 3, London, Shaw and Sons, 1925, p. 186.

[5] Bay, E. B., and Adams, W.: Possible intranodal block. A report of cases. Am. Heart J. **7:** 759, 1932.

[6] Condorelli, L: Experimentelle Untersuchungen über die interaurikuläre Reizleitung. Ztschr. ges. exper. Med. **68:** 516, 1929.

[7] Lombardini, R. V., and Aviles, M.D.: La interferencia el doble comando y los ritmos parciales. Dos casos de flutter auricular parcial simultaneos con el ritmo sinual que por momentos interfieren sus estimulos. Rev. argent. de cardiol. **5:** 380, 1939.

[8] Bellet, S.: Clinical Disorders of the Heart Beat, Philadelphia, Lea and Febiger, 1953, p. 132–34.

[9] Moreira, J. A.: Dissociacao inter-auricular completa. Un caso de arithmia completa por fibrilo-flutter con una serie de ondas P de ritmo regular. Clin. contemporan. **5:** 328, 1951.

[10] Dagnini, G.: L'attivita auricolare pre fibrillatoria. Cuore e circolaz. **21:** 571, 1937.

[11] De Castro, O.: Nouveaux aspects de la pathologie auriculaire. Fibrillation et flutter partiels. Arch. mal. coeur **30:** 207, 1937.

[12] Mahaim, I.: De l'anévrisme primitif de l'oreillette gauche, troubles particuliers du rythme cardiaque; la dissociation inter-auriculaire. Ann. d. méd. **21:** 380, 1927.

[13] Kure, K., and Kaneko, H.: Ein Fall von Dissoziation der beiden Vorhofskontraktionen mit dem Kammersystolenausfall. Klin. Wchnschr. **5:** 1923, 1926.

[14] Scherf, D., and Siedek, H.: Über Block zwischen beiden Vorhöfen, Ztschr. klin. Med. **127:** 77, 1934.

[15] Rothberger, C. J., and Scherf, D.: Zur Kenntnis der Erregungsausbreitung vom Sinusknoten auf den Vorhof. Ztschr. ges. exper. Med. **53:** 792, 1927.

[16] Hertz, J.: A case of double auricular action with one-sided block. Acta med. Scandinav. **101:** 409, 1939.

[17] Lewis, T., Drury, A. N., and Ilescu, C. C.: Some observations upon atropine and strophanthin. Heart **9:** 21, 1921.

[18] Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias. Springfield, Ill. Charles C Thomas, 1952.

[19] Lian, C., and Golblin, V.: Un cas de double rhythme auriculaire par dissociation inter-auriculaire. Arch. mal. coeur **31:** 52, 1938.

[20] Decherd, G. M., Ruskin, A., and Brindley, P.: Interatrial and sinoatrial block, with an illustrative case. Am. Heart J. **31:** 352, 1946.

[21] Luisada, A. A.: Heart. Ed. 2, Baltimore, Williams and Wilkins Co., 1954, p. 383.

[22] Scherf, D., and Boyd, L. J.: Clinical Electro-

cardiography, St. Louis, C. V. Mosby Co., 1941, p. 296.

[23] WHITE, P. D.: Heart Disease. Ed. 4, New York, Macmillan, Co., 1951, p. 931.

[24] GÉRAUDEL, E.: La double commande; étude des tracés où coexistent deux commandes indépendantes, l 'une auriculoventriculaire, l 'autre auriculair. Arch. mal. coeur **28:** 121, 1935.

[25] DOMINGUEZ, C., AND BIZZOZERO, R. C.: Double commande auriculaire. Arch. mal. coeur **30:** 820, 1937.

[26] DUCLOS, F.: Un caso de "doble mano auricular." Arch. cardiol. y hemat. **16:** 175, 1935.

[27] KATZ, L. N.: Electrocardiography. Ed. 2. Philadelphia, Lea and Febiger, 1946, p. 772.

[28] BACHMANN, G.: The inter-auricular time interval. Am. J. Physiol. **41:** 309, 1916.

[29] TAIT, J.: The action of yohimbine on the heart, with special reference to toxic heart-block. Quart. J. Exper. Physiol. **3:** 185, 1910.

[30] BURGHARD, E., AND WUNNERLICH, A.: Das Elektrokardiogramm des Säuglings, des Neugeborenen, und des Frühgeborenen. Ztschr. Kinderh. **45:** 56, 1927.

[31] KERR, W. J., AND SAMPSON, J. J.: Functional longitudinal block in the human heart. A probable case with unusual arrhythmia, Am. Heart J. **7:** 574, 1932.

[32] LAUFER, S.: Zum Studium der Reizleitungsstörungen im Vorhof mittels direkter Ableitung des Vorhofelektrokardiogramms. Ztschr. klin. Med. **127:** 678, 1935.

[33] —, AND RUBINO, A.: Sull'importanza delle derivazioni elettive nella diagnosi dei disturbi di conduzione del miocardio atriale. Clin. med. Ital. **67:** 365, 1936.

[34] RUBINO, A.: Fluttuazioni e fibrillazioni parziali degli atria documentate col sistema delle derivazioni elettive. Cuore e circolaz. **20:** 57, 1936.

[35] SOSSAI, A.: Ricerche cliniche sulla specificita della derivazione esofagea per la registrazione dell' elettrogramma dell'atrio sinistro. Cuore e circolaz. **22:** 441, 1938.

Medicine, and this is one of the most valuable of the teachings of history, cannot remain equal to its great task without preserving for the physician his double character of scientist and worker for the people, according to the classic concept. If in the exercise of his art he is guided by his knowledge of the laws of nature, then his technical knowledge, his calm judgment, and his objective reasoning should furnish him with the rules which will determine the application of these natural laws in practice. It is only thus that the clinician can be clinical in the true sense of the word.—ARTURO CASTIGLIONI (1874–).

Heparin-Activated Clearing Factor

Standardized Test, Agewise Application, and Clinical Observations

By SAUL P. BAKER, M.D.

A possible relationship may exist between the concentration of heparin-activated plasma clearing factor and alterations in lipid metabolism associated with advancing age, atherosclerosis, and other diseases. To test this hypothesis, 121 men were evaluated in the development and application of a standardized *in vitro* method for the determination of clearing factor response to minimal heparin stimulation. Eighty-four men, ranging from 21 to 93 years, selected from this group, were evaluated in an age-wise study. Patients with diagnoses of recent myocardial infarction (presumptive evidence of coronary atherosclerosis), cirrhosis of the liver, and chronic alcoholism were also tested.

DURING the past 6 years, many studies of lipid metabolism and its derangements have been concerned with a clearing factor evoked in blood plasma by the *in vivo* injection of heparin. Since the observation that heparin administration clears the turbidity of alimentary lipemic plasma,[1] many investigators have sought to elucidate its mechanisms.[2-7] Clearing factor has been identified as a plasma lipase, now called "lipoprotein lipase,"[8, 9] which hydrolyzes the triglyceride of lipoproteins or fat emulsions, reducing it to free fatty acid and glycerol.[2, 5] A linear relationship has been observed during the initial *in vitro* clearing of a standard fat emulsion by heparin-activated plasma and the release of free fatty acid.[3, 4] Furthermore, it has been shown that the rate of *in vitro* clearing of a fat emulsion is proportional to the concentration of clearing factor present, and that the *in vitro* clearing activity of postheparin plasma may be quantitatively accounted for on the basis of its lipolytic activity.[3, 4]

In view of the possible relationship of plasma clearing factor concentration to atherosclerosis and other diseases associated with alterations in lipid metabolism, clearing factor response has been extensively investigated in man.[10-14] Similarity between possible alterations in lipid metabolism with advancing age and atherosclerosis has been suggested by experiments in which standard fat meals were administered to young and old subjects[15, 16] and to patients with coronary atherosclerosis.[10, 11, 13] Both the old subjects and those with atherosclerosis demonstrated prolonged high levels of alimentary chylomicronemia[15] and lipemia.[13, 16] Heparin injection after a standard fat meal, in one study, demonstrated a decreased clearing response in patients with coronary atherosclerosis,[10] and in another study, no decrease in clearing response in atherosclerotic subjects[11] as compared to controls. In a third report,[13] heparin was found to accelerate the clearing of alimentary lipemia in normal subjects and to initiate the clearing response in subjects with coronary atherosclerosis after a standard fat meal.

When fasting subjects with coronary atherosclerosis, the nephrotic syndrome, and idiopathic hyperlipemia were evaluated with respect to their clearing factor response,[12] the normal control subjects demonstrated the greatest clearing; the patients with atherosclerosis slightly less; and the nephrotic and idiopathic hyperlipemic subjects considerably less clearing. Another observer[14] found a variable clearing factor response in atherosclerotic patients, normal or elevated clearing in young subjects, and decreased or absent clearing in old subjects or those suffering from precocious senility. Although one study[17] demonstrated significantly lower blood lipase levels in older people than in the young, these same investigators[15] found no appreciable difference in the disappearance rate of chylomicrons following

From the Gerontology Branch, National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

intravenous injection of fatty plasma in old subjects as compared to young subjects.

Inasmuch as no uniform technic or heparin dosage was employed to determine clearing factor response to heparin stimulation in the various studies cited above, results of these investigations cannot be compared with each other. The research reported here was designed to analyze various factors in the development of a standardized *in vitro* assay method for the evaluation of clearing factor response to minimal heparin stimulation in man and to apply this method to a study of possible age differences in clearing factor response in men. Observations were also made on patients with recent myocardial infarction and cirrhosis of the liver.

Material and Methods

One hundred and twenty-one men were selected from the population of the Infirmary Division (Old Peoples' Home) and from convalescent patients of the Baltimore City Hospitals. These were utilized in the analysis of various factors in the development of a standardized *in vitro* assay method for the determination of clearing factor response to minimal heparin stimulation. From this group, 84 men, ranging from 21 to 93 years of age, were selected for an evaluation of possible age differences in clearing factor response. All subjects were afebrile, free from evident acute infection, and on ward diet for at least 1 week prior to test. None had evidence of recent myocardial infarction, congestive heart failure, clinical jaundice, uncontrolled diabetes mellitus, the nephrotic syndrome, or had received heparin within 1 week prior to study. No attempt was made to identify subjects with or without atherosclerosis, in view of the improbability of completely excluding this disease in any subject in the age group studied. Tests were also performed on 7 subjects with a diagnosis of recent myocardial infarction and 6 subjects with a diagnosis of cirrhosis of the liver.

Heparin Sodium, 3 mg. in 5 ml. of isotonic saline* injected intravenously, was used as the clearing factor stimulus. Control and 8-minute postheparin blood samples (25 ml.) were obtained from all subjects after an overnight fast (at least 12 hours). Blood samples were immediately mixed with dried sodium oxalate (1 mg./ml. blood) and cooled to 0 C. in an ice bath. The plasma was separated by centrifugation at 0 C. It was subsequently kept at 0 C. or frozen until used. Substrate consisted of a 1 per cent emulsion of coconut oil (Ediol)† freshly prepared with distilled water. Three tenths of a milliliter of this emulsion was added to and thoroughly mixed with a 4.5 ml. aliquot of postheparin plasma, which had been previously incubated for 10 minutes in a water bath at 30 ± 1 C. This proportion, in general, gave an initial optical density reading between 0.600 and 0.700 against distilled water on the Beckman Model DU Spectrophotometer, with microcuvettes (3 by 10 by 25 mm.) at 6500 Å. The postheparin plasma-fat emulsion mixture was kept in the 30 C. water bath for 1 hour. During this time, optical densities were read every 5 minutes on 0.3 ml. aliquots of the mixture. Optical densities of control plasma and control plasma-fat emulsion mixtures were similarly determined. A graph of optical density versus time was then plotted for each sample. To this plot, a straight line was visually fitted at the section demonstrating the greatest rate of change in optical density. The negative slope of this line, k, (decrease in optical density per hour), was taken to represent the rate of clearing of postheparin plasma.

In preliminary studies, heparin dosage, state of alimentation, time of postheparin blood sample, effect of temperature on rate of clearing, type of substrate used, and the effect of room temperature on clearing factor activity were evaluated. An analysis of the method presented here included its reproducibility, proportionality between k and clearing factor concentration, effect of freezing and storing at 0 C. on clearing factor activity, and biological variability. Reproducibility was determined by simultaneous duplicate runs on aliquots of 52 postheparin plasmas. Proportionality between k and clearing factor concentration was tested by determining calculated versus observed k's for 57 mixtures of postheparin plasmas and 28 mixtures of postheparin and control plasmas. Effects of freezing and storing at 0 C. on clearing factor activity were tested in 3 categories. Forty postheparin plasma samples were frozen and stored for 1 day to 2 weeks, k first being determined on the fresh plasma. Fifty-three mixtures of postheparin plasmas and 66 mixtures of postheparin plasma with control plasma were similarly tested after freezing and storing for 1 day to 8 weeks. Biological variability was determined by repeat runs, at least 1 week apart, on 34 subjects.

Results

Figure 1 illustrates the graphic determination of k for high, intermediate, and low k's. In testing reproducibility of the method, simultaneous duplicate runs on aliquots of 52 postheparin plasmas yielded a standard error of the mean $k = \pm 0.05$, $r = 0.98$. A scatter plot of

* The author wishes to acknowledge the courtesy of Dr. E. A. Hawk of the Upjohn Company in supplying the heparin for this investigation.

† Ediol was kindly supplied by Mr. Stanley J. Schapiro of Schenley Laboratories, Inc.

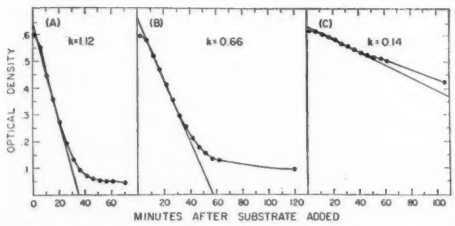


FIG. 1. Relation between optical density and time expressed as rate of clearing, k, (decrease in optical density per hour) of mixtures of postheparin plasma and fat emulsion. Readings of optical density have been corrected for control plasma in each case (Control O.D. = 0.082, 0.080, and 0.063, respectively). High (A), intermediate (B), and low (C) k's are illustrated (k = 1.12, 0.66, and 0.14, respectively).

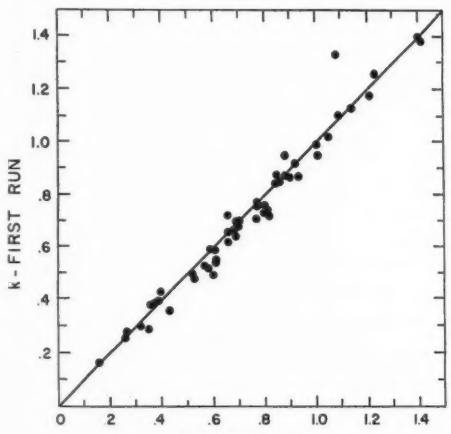


FIG. 2. Reproducibility of the method. Simultaneous duplicate runs on aliquots of 52 postheparin plasmas. Standard error of mean $k = \pm 0.05$, $r = 0.98$.

duplicate runs is shown in figure 2. Observations on the proportionality between k and clearing factor concentration for 57 mixtures of postheparin plasmas indicated a standard error of the mean $k = \pm 0.10$, $r = 0.95$, when calculated k's were compared with observed k's. Twenty-eight mixtures of postheparin plasma and control plasma similarly evaluated yielded a standard error of the mean $k = \pm 0.08$, $r = 0.94$. Effects of freezing and storing at 0 C. on clearing factor activity were as follows: 40 postheparin plasma samples frozen and stored for 1 day to 2 weeks gave a standard

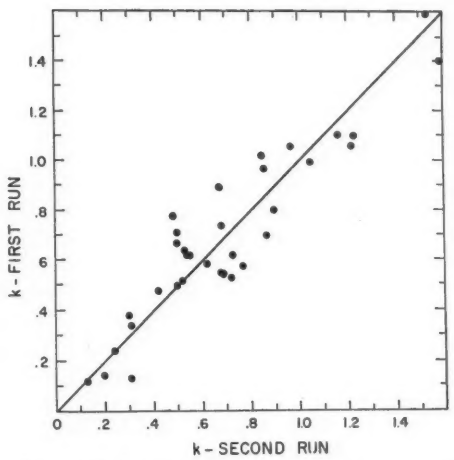


FIG. 3. Biological variability. Repeat runs on 34 subjects at least 1 week apart. Standard error of mean $k = \pm 0.13$, $r = 0.93$.

error of the mean $k = \pm 0.14$, $r = 0.93$; 53 mixtures of postheparin plasma frozen and stored for 1 day to 8 weeks yielded a standard error of the mean $k = \pm 0.11$, $r = 0.93$; and 66 mixtures of postheparin plasma with control plasma similarly tested after freezing and storing gave a standard error of the mean $k = \pm 0.09$, $r = 0.90$. Biological variability in 34 subjects tested by repeat runs at least 1 week apart yielded a standard error of the mean $k = \pm 0.13$, $r = 0.93$. A scatter plot of repeat runs is shown in figure 3.

Eighty-four men, evaluated as an agewise sample (21 to 93 years) for clearing factor response, demonstrated a mean k of 0.74, σ_d = 0.29. Mean age was 61.3 years, σ_d = 17.8. Range of k in this group was from 0.13 to 1.40. Eight subjects demonstrated k greater than 1.10. The 3 youngest of these (32, 42, and 51) all had diagnoses of chronic alcoholism. Of the remaining 5 subjects (68, 77, 78, 80, and 89), none had been diagnosed as a chronic alcoholic. Incidence of alcoholism in the 76 subjects with $k \leqq 1.10$ was not determined. It is interesting to note that the 68-year-old subject (k = 1.22) developed an acute myocardial infarction 8 weeks after being tested for clearing factor response.

Table 1 presents the mean k for each decade.

TABLE 1.—*Agewise Distribution of Clearing Factor Response by Decades*

Age group	Number of subjects	Mean age	Mean k	$\sigma_d k$
20–29	3	21.0	.58	.53 to .66 (range)
30–39	7	33.4	.64	.35
40–49	11	44.5	.75	.25
50–59	15	53.7	.72	.25
60–69	18	64.9	.70	.34
70–79	14	73.5	.80	.31
80–89	14	84.1	.86	.25
90–99	2	92.5	.56	.28 to .84 (range)
Entire Group (21 to 93 years)	84	61.3	.74	.29

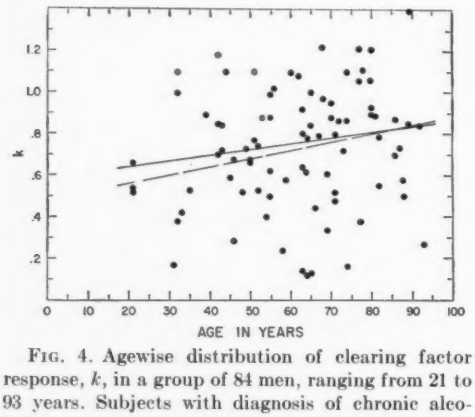


FIG. 4. Agewise distribution of clearing factor response, k, in a group of 84 men, ranging from 21 to 93 years. Subjects with diagnosis of chronic alcoholism are represented by an x. Agewise regression for the entire group of 84 is indicated by the solid line. Agewise regression for 80 subjects, excluding 4 with diagnosis of chronic alcoholism, is indicated by the broken line.

Except for the 2 subjects over 90 years, there appears to be a slight over-all increase of mean k with age in this sample. Figure 4 shows the individual k's as a scatter plot versus age. Agewise regression lines have been drawn with and without including 4 young subjects (32, 42, 51, and 53) with diagnoses of chronic alcoholism. The apparent increase of k with age is not statistically significant when the alcoholics are included. When they are omitted, however, the regression of k on age becomes significant at $p < 0.02$. The mean increase of k per decade in this instance is 0.04.

When 7 patients with recent myocardial infarction (mean $k = 0.74$) were compared with subjects evaluated agewise in the same age decades (40 to 69 years, mean $k = 0.69$), no significant difference was observed.

None of the 84 subjects in the agewise sample had been diagnosed as having cirrhosis of the liver. One patient with clinical jaundice due to hepatic cirrhosis, separately examined, yielded a $k = 1.60$. Consequently, 5 other patients with cirrhosis of the liver, all with clinically manifest jaundice, were separately evaluated. Their mean k was found to be 1.01. When this group was combined with the 4 chronic alcoholics (mean $k = 1.09$), and examined as a group of 10 (mean $k = 1.04$), they were found to differ significantly ($p < 0.01$) from the agewise sample (mean $k = 0.67$) in the same decades (30 to 69 years).

DISCUSSION

In attempting to establish individual differences in clearing factor response in man, a standardized method would appear to be essential. Development of such a method involved the consideration of several parameters. In previous studies, heparin dosage ranged from 3 to 100 mg. or more.[10-14] Although the heparin dosage falling within the physiologic dose-response curve may vary with the species,[3, 6, 7, 10] 3 mg. of heparin yields a suitable submaximal physiologic stimulus level in man. Under the standardized conditions of the study discussed here, with 3 mg. of heparin, no relationship was observed between body weight and clearing factor response, although weights varied over a wide range. The state of alimentation also has varied. Some studies[12] were performed on fasting subjects, while others[10, 11, 13] were performed after standard fat meals. Variability in postprandial lipemia made it desirable to use subjects after an overnight fast (at least 12 hours). The substrate employed in various investigations has varied from an alimentary lipemic plasma produced by various standard fat meals[10-13] to standard fat emulsions.[3, 4, 6]

A standard coconut oil emulsion (Ediol) employed by one group of investigators[4] was used in this study. Time of postheparin blood

sampling has differed. In studies on plasmas obtained 8, 15, and 30 minutes after heparin administration, the greatest clearing factor response was generally obtained in the 8-minute sample. Lesser clearing activity was observed in the 15- and 30-minute samples; activity decreasing with increasing time after injection. Consequently, an 8-minute postheparin blood sample was chosen to obtain an estimate of the height of clearing factor response. No temperature control is indicated in many previous studies, although the enzymatic nature of the reaction would appear to make this obligatory. Effect of temperature on rate of clearing was investigated and a Q_{10} of about 1.4 was found. A temperature of 30 ± 1 C. was therefore selected as producing a convenient intermediate rate of clearing within the range of temperature found in the laboratory. Clearing factor activity decreased when postheparin plasma was allowed to stand at room temperature. Thus, after 2 hours at 25 C., clearing factor activity had attenuated approximately 30 per cent. Consequently, all plasma was extracted at 0 C. and kept at 0 C. until used.

Although 25 ml. of blood were used in these studies, several parameters being evaluated on aliquots of the same plasma, the test may be performed with 10 ml. of blood or less, 3.0 ml. of postheparin plasma being required.

In this *in vitro* test, if the fat emulsion substrate is acted upon by an enzyme system and the optical density at 6500 Å is a measure of the concentration of fat emulsion present, the optical density of the mixture would decrease at a constant rate determined by enzyme concentration as long as excess substrate was present. Under these circumstances, this rate could be determined by noting the change in optical density in a given period of time,[10] or the time required for given change in optical density.[3] The negative slope of a plot of optical density versus time is not constant, but may increase to a maximum in 0 to 60 minutes, and decrease subsequently, or approach an asymptote. The approximately constant maximal rate of change, usually of the midportion of the curve, has been used and is shown to be well reproducible. This is closer to the maximal rate than the mean rate of change for the period of observation, or the time required for a given change in optical density, and provides a wider spread of values than the use of only 2 points.

It is recognized that clearing factor may act simultaneously upon both an exogenous standard fat emulsion that contributes turbidity and an endogenous nonturbid lipoprotein-linked triglyceride. However, it is suggested that the endogenous lipoprotein-linked triglyceride per se does not exert an appreciable influence upon the initial rate of clearing of fat emulsion. This is postulated in view of the observations[4] that there is a constant ratio (1.4:1.0) between per cent change in optical density to per cent of coconut oil total fatty acid released in free form, and that the amount of free fatty acid released during clearing never reached the total amount of coconut oil fatty acid added to the incubation mixture even when clearing was complete and the optical density of the mixture had returned to control levels. Thus, even the exogenous fat emulsion substrate is probably not completely hydrolyzed during the initial clearing reaction. Under the standardized conditions of the study discussed here, it is suggested that there is excess albumin to act as a fatty acid acceptor, even in cases of hypoalbuminemia. This is postulated in view of the fact that in cirrhotic patients with severe parenchymal liver damage, hypoalbuminemia, and marked inversion of the albumin:globulin ratio, rapid clearing progresses as a linear rate of change of optical density with time. Furthermore, even assuming a hypoalbuminemia of 2 Gm. per 100 ml. of plasma in the *in vitro* system used in these studies, the exogenous fat emulsion substrate is of the order of 3 mg., while the amount of albumin available as fatty acid acceptor is of the order of 90 mg. In other circumstances, where the hypoalbuminemia is accompanied by marked endogenous hyperlipemia, it is conceivable that conditions for an *in vitro* clearing reaction may not be optimal. This may be the result of either an initially high optical density of the plasma due to visible endogenous lipemia or to lack of sufficient free fatty acid acceptor or both. In such cases, appropriate modification of the *in vitro* clearing system might be considered.

No evidence was obtained in this study to in-

dicate a decrease in intravascular clearing factor response, either in old subjects or in patients with recent myocardial infarction. Consequently, it would appear unlikely that the persistent lipemia[13, 16] and chylomicronemia,[15] which have been reported for old subjects[15, 16] and patients with coronary atherosclerosis[13] after a standard fat meal, are due to an intravascular deficiency or absence of clearing factor or its precursors. Clearing factor response can be evoked by minimal intravenous exogenous heparin stimulation in these subjects to at least the same degree as that found in young subjects or subjects without recent myocardial infarction. Evidence indirectly implicating the gastrointestinal tract is found in the equal response of old and young subjects with respect to disappearance rate of chylomicrons following intravenous injection of fatty plasma[15] and the 21 per cent decrease in pancreatic lipase in old versus young men.[18] Further information suggesting gastrointestinal involvement is supplied by the observation that intravenous infusion of a fat emulsion evokes a decrease in serum lipids and changes in their electrophoretic pattern in normal human subjects during alimentary lipemia, in patients with idiopathic hyperlipemia, and in dogs.[19] These alterations appear to be identical with those produced in serum lipids by intravenous heparin injection. Thus, while intravenously administered fatty plasma or fat emulsions may produce adequate clearing and hydrolysis of triglyceride, endogenous production of clearing factor in response to the stimulus of a fatty meal via the gastrointestinal tract may be impaired in old subjects, in patients with coronary atherosclerosis, and perhaps also in patients with idiopathic hyperlipemia.

The increased k obtained in 10 patients with diagnoses of chronic alcoholism or cirrhosis of the liver supports another report[14] of a greatly increased clearing factor response in a subject with ethanolic cirrhosis of the liver. Perfusion experiments in rats,[20] wherein citrated plasma was mixed with heparin and perfused through the isolated hind limbs, the lungs, and all of the abdominal viscera drained by the portal vein, demonstrated clearing factor production in each instance. The liver, however, produced no clearing factor upon such perfusion. Furthermore, perfusion of postheparin plasma (containing active clearing factor) through the liver resulted in a decrease in its clearing activity. Also, in rats injected with heparin, blood from the inferior vena cava, portal vein, and aorta had similar clearing activity, while that from the hepatic vein demonstrated less clearing activity than that of the aortic blood. It is, therefore, suggested that one cause of the increase in clearing factor activity found in the postheparin plasma of some subjects may be a decrease in the functional capacity of the liver parenchymal cells to remove or inactivate clearing factor.

Although no common diagnosis or pathologic etiology could be discovered for the 5 subjects in the sample of 84 that gave k's less than 0.20 (31, 63, 64, 65, and 74 years old, respectively), a patient separately examined who was suffering from anemia due to gastrointestinal bleeding demonstrated a $k = 0.13$. Furthermore, a patient developing active pulmonary tuberculosis had progressively lower k's on repeat examinations several weeks apart. Another patient with initially low k demonstrated an increase in k upon convalescence from an acute exacerbation of his chronic renal disease. These observations support the report[14] of absence or decrease in clearing factor response in infections, fevers, and anemia, clearing factor response reappearing with convalescence in certain instances.

Summary and Conclusions

A standardized *in vitro* method for the evaluation of clearing factor response to minimal heparin stimulation in man has been developed. This method supplements, modifies and incorporates various features of tests now in use and critically analyzes some of the factors involved. Reproducibility and biological variability of the method have been determined.

Rate of clearing, k, (decrease in optical density per hour) was found to have a standard error on repeat runs on the same subject of $\pm 0.13\ k$. Evidence has been presented suggest-

ing that the rate of clearing, k, is proportional to the concentration of clearing factor present. Freezing and storage at 0 C. produced no appreciable attenuation of clearing factor activity.

Clearing factor response to minimal heparin stimulation was determined in an agewise study of 84 men, ranging from 21 to 93 years. No statistically significant agewise regression was found, although a tendency toward an increase in clearing factor response with age was present.

Four young subjects diagnosed as chronic alcoholics had a mean high k, 3 of these having the highest k's in the 21–59 age group. Six additional patients with cirrhosis of the liver also had a mean high k value. Liver pathology, either subclinical or clinical, may account for these high k values.

Seven patients with recent myocardial infarction (presumptive evidence of coronary atherosclerosis) demonstrated no lesser clearing factor response to intravenous heparin stimulation than did subjects who were not known to have had a recent myocardial infarction.

Acknowledgment

The author acknowledges with thanks the helpful criticism and review of the manuscript by Dr. Nathan W. Shock and Dr. Milton Landowne; the helpful criticism of Dr. Charles Barrows; the technical assistance of Mr. James Robinson, and the computational assistance of Mrs. Elizabeth Benser.

Summario in Interlingua

Esseva disveloppate un methodo standardisate pro le evalutation in vitro del responsa del factor de clarification al stimulation per heparina in quantitates minimal in subjectos human. Iste methodo supplementa, modifica, e incorpora in se varie aspectos del tests nunc in uso e analysa criticamente alicunes del factores implicate. Le reproducibilitate e le variabilitate biologic del methodo ha essite determinate.

Le clarification, exprimite como k e definite como reduction del densitate optic per hora, esseva determinabile per le methodo con un error standard, establite per repetitiones del tests pro subjectos individual, de $\pm 0{,}13$ k. Es presentate datos que pare provar que le clarification per unitate de tempore es proportional al concentration del factor de clarification. Refrigeration e immagasinage a 0 C non resultava in appreciabile reductiones del activitate del factor de clarification.

Le responsa del factor de clarification al stimulation per heparina in quantitates minimal esseva determinate, con referentia al etate del subjectos, in 84 homines de inter 21 e 93 annos de etate. Esseva trovate nulle statisticamente significative regression con le avantiamento del etate, sed le gruppo studiate monstrava un tendentia del responsa del factor de clarification de augmentar se con le avantiamento del etate del subjectos.

Quatro juvene subjectos, diagnosticate como alcoholicos chronic, habeva alte valores medie pro k. Tres de illes habeva le plus alte valores pro k in le gruppo de etates de inter 21 e 59 annos. Sex altere patientes con cirrhosis del hepate habeva etiam alte valores medie pro k. Morbo hepatic, clinic o subclinic, representa possibilemente un explication de iste alte valores pro k.

Septe patientes con recente infarcimento myocardial (reguardate como prova presumptional de atherosclerosis coronari) non monstrava plus basse responsas del factor de clarification al stimulation per heparina intravenose que subjectos sin evidentia de recente infarcimentos myocardial.

REFERENCES

[1] Hahn, P. F.: Abolishment of alimentary lipemia following injection of heparin. Science **98:** 19, 1943.

[2] Anfinsen, C. B., Boyle, E., and Brown, R. K.: The role of heparin in lipoprotein metabolism. Science **115:** 583, 1952.

[3] Grossman, M. I.: The quantitative measurement of heparin-induced lipemia clearing activity of plasma. J. Lab. & Clin. Med. **43:** 445, 1954.

[4] —, Stadler, J., Cushing, A., and Palm, L.: Relation of lipolysis to deturbidification and returbidification in heparin-induced lipemia-clearing phenomenon. Proc. Soc. Exper. Biol. & Med. **88:** 132, 1955.

[5] Brown, R. K., De Lalla, L. S., and Kauffman, D. L.: Serum lipoproteins. Clin. Chem. **1:** 83, 1955.

[6] Meng, H. C., Hollett, C., and Cole, W. E.:

Some factors affecting the clearing of neutral fat emulsion by post-heparin plasma. Am. J. Physiol. **179:** 314, 1954.

[7] SPITZER, J. J.: Properties of heparin-produced lipemia clearing factor. Am. J. Physiol. **171:** 492, 1952.

[8] KORN, E. D.: Clearing factor, a heparin-activated lipoprotein lipase. I. Isolation and characterization of the enzyme from normal rat heart. J. Biol. Chem. **215:** 1, 1955.

[9] —: Clearing factor, a heparin-activated lipoprotein lipase. II. Substrate specificity and activation of coconut oil. J. Biol. Chem. **215:** 15, 1955.

[10] BLOCK, W. J., BARKER, N. W., AND MANN, F. D.: Effect of small doses of heparin in increasing the translucence of plasma during alimentary lipemia: Studies in normal persons and patients having atherosclerosis. Circulation **4:** 674, 1951.

[11] HOOD, B., ANGERWALL, G., ISAKSSON, B., AND WELIN, G.: Studies on heparin and the lipemia clearing factor. I. Scandinav. J. Clin. & Lab. Invest. (Oslo) **6:** 1, 1954.

[12] HERZSTEIN, J., WANG, CHUN-I, AND ADLERSBERG, D.: Effect of heparin on plasma lipid partition in man: Studies in normal persons and in patients with coronary atherosclerosis, nephrosis, and primary hyperlipemia. Ann. Int. Med. **40:** 290, 1954.

[13] WOLDOW, A., CHAPMAN, J. E., AND EVANS, J. M.: Fat tolerance in subjects with atherosclerosis; heparin effects upon lipemia, lipoproteins and gamma globulin. Am. Heart J. **47:** 568, 1954.

[14] KAUFMANN, H.: Étude clinique du facteur d'eclaircissement. Presse méd. (Paris) **63:** 1045, 1955.

[15] BECKER, G. H., MEYER, J., AND NECHELES, H.: Fat absorption in young and old age. Gastroenterology **14:** 80, 1950.

[16] HERZSTEIN, J., WANG, CHUN-I, AND ADLERSBERG, D.: Fat loading studies in relation to age. Circulation **8:** 450, 1953.

[17] BECKER, G. H., MEYER, J., AND NECHELES, H.: Fat absorption and atherosclerosis. Science **110:** 529, 1949.

[18] NECHELES, H., PLOTKE, F., AND MEYER, J.: Studies in old age. V. Active pancreatic secretion in the aged. J. Digest. Dis. **9:** 157, 1942.

[19] HERBST, F. S. M., LEVER, W. F., AND WADDELL, W. R.: Effects of intravenously administered fat on the serum lipoproteins. Science **123:** 843, 1956.

[20] JEFFRIES, G. H.: The sites at which plasma clearing activity is produced and destroyed in the rat. Quart. J. Exper. Physiol. (London) **39:** 261, 1954.

Bergy, G. G., Burroughs, R. W., and Bruce, R. A.: Effects of Cortisone on Metabolic Responses in Myocardial Infarction. Am. J. M. Sc. **232:** 513 (Nov.), 1956.

Five patients with myocardial infarction received cortisone within 48 hours of the onset of the attack in doses of 75 mg. orally every 6 hours decreasing to 25 mg. daily after the twelfth day. The usual supportive measures were employed, including pressor agents in 1 patient with shock. Anticoagulants were not used. Electrolyte and water balance measurements were obtained during the course of treatment. Neither morbidity nor mortality was influenced by cortisone therapy in this small group. Death occurred in 2 patients as predicted by the Pathologic Index Rating on admission. The treatment had no stabilizing effect upon blood pressure and did not prevent hypotension. Moderate sodium and water retention occurred in the 2 patients who died, but did not occur in the 3 patients who survived.

SHUMAN

Cancellation of Esophageal Electrocardiograms

By RALPH F. MORTON, M.D., WILLIAM E. ROMANS, B.S., AND DANIEL A. BRODY, M.D.

Cancellation of juxtacardiac esophageal electrocardiograms, as demonstrated in this study, indicates certain limitations of the equivalent cardiac dipole hypothesis. A new and more fundamental theory developed here shows that in large measure cancellation occurs because the cancellation network is in effect a relatively insensitive electrocardiographic connection, and because there is always prior assurance that a given complex can be completely canceled at any 2 desired instants during the cycle. The new theory also explains the paradox that proximity electrocardiograms can be canceled even though local action currents exert a relatively powerful influence on such leads.

CANCELLATION of body surface electrocardiograms in health and disease has been abundantly demonstrated during the past few years.[1-3] One possible explanation of the cancellation phenomenon is that the effective behavior of the electromotive forces of the heart is essentially that of a single, fixed-location current dipole. Frank,[4] in support of such an equivalent cardiac dipole hypothesis, demonstrated that the electrocardiographic potentials on the body surface of a single subject were approximately dipolar in distribution. He showed further that numerous pairs of electrocardiographic mirrors were very nearly located diametrically opposite each other in image space from the electric center of a model patterned from the subject.[5]

Despite this striking evidence in support of the equivalent cardiac dipole hypothesis, it occurred to us that other physical factors may play an important role in the cancellation phenomenon, and that it might even be possible to obtain cancellation of electrocardiograms derived from regions that are in extreme proximity to the heart. In order to explore this possibility we undertook a systematic search for mirror patterns of electrocardiograms recorded from the juxtacardiac region of the esophagus. It is this study that forms the experimental basis of the present report.

METHODS AND MATERIALS

Patients from the medical service of our teaching hospital were employed in this study. None of them had cardiac disease, and all were in relatively good physical condition except for 1 who suffered from moderately severe pulmonary emphysema. A previously described esophageal electrode[6] was passed pernasally and advanced down the esophagus until a transitional QRS electrocardiogram was obtained with respect to a terminal formed by tieing the left arm and leg together through matched 68,000-ohm resistors. A suction cup electrode, 15 mm. in diameter, was applied to various regions of the torso until a reasonably good mirror of the esophageal QRS complex was obtained. With a 500,000-ohm potentiometer connected between the esophageal and search electrodes, Schmitt's cancellation procedure[1] was pursued until optimum results were obtained. The procedure was repeated with the tip of the esophageal tube located 4 cm. distally and proximally from the point of transitional QRS registration. In addition, cancellation of the right arm potential was performed in order to provide reference values and to check upon the quality of our technic.

Because of discomfort due to the presence of the esophageal tube, the cancellation procedure could not be completed at all 3 esophageal levels in some of the subjects. Cancellation from the infratransitional position was performed 24 times, once in each of 22 subjects, and twice in 1 subject. Cancellation from the transitional position was performed 25 times, once in each of 17 subjects, and twice in each of 4 subjects. Cancellation from the supratransitional level was performed 29 times, once in each of 21 subjects, and twice in each of 4 subjects. The right arm potentials were cancelled once in each of 23 subjects.

Cancellation coefficients were calculated from the equation

$$c = 50r(1/R + 1/S)\%,$$

where c is the cancellation coefficient, and r, R, and S are the peak-to-peak amplitudes, respectively, of the QRS complexes in the cancellation, reference, and search electrocardiograms. This formula, although different in form from Schmitt's formula,[1] is virtually equivalent to it.

From the Cardiovascular Laboratory, Department of Medicine, University of Tennessee, and the John Gaston Hospital, Memphis, Tenn.

This study was supported by research grant H-1362(C3) of the National Heart Institute.

Results

A typical cancellation for each of the 3 esophageal levels that we explored is shown in figure 1. The QRS complexes were generally diphasic with an initial negativity and terminal positivity. The deflections were predominantly positive at the infratransitional level, equiphasic at the transitional level, and predominantly negative at the supratransitional level. The esophageal tracings were recorded with reversed polarity in order to facilitate recognition of their mirror patterns during exploration of the body surface.

Nineteen mirror locations of the infratransitional level occurred very nearly on the right midclavicular line between the clavicle and the fourth rib, 2 occurred anteriorly over the right shoulder joint, 1 in the right supraclavicular fossa, 1 over the spinous process of the right scapula, and 1 over the seventh rib in the right anterior axillary line. All of the mirror locations of the transitional esophageal level were clustered on the left midclavicular line between the fourth and sixth ribs, except for 2 that were located in the first interspace halfway between the left sternal margin and midclavicular line, and 2 in the third interspace slightly medial to the left midclavicular line. All except 3 mirror locations of the supratransitional level were found in an area on the left chest wall that was bounded by the fifth and ninth ribs, and the midclavicular and midaxillary lines. The remaining 3 locations occurred at the same level but between the midaxillary and posterior axillary lines.

A statistical analysis of the results is summarized in figure 2 and table 1. The control studies on the right arm potentials provided the best cancellations of all, with an average cancellation coefficient of 6.1 per cent and a standard deviation of 5.5 per cent. In decreasing order of excellence, average cancellation coefficients of 9.3, 11.2, and 13.5 per cent were found at the supratransitional, infratransitional, and transitional levels, respectively. The standard deviations were 4.6, 8.3, and 7.9 per cent, respectively. Of the whole group only one attempt resulted in no cancellation (can-

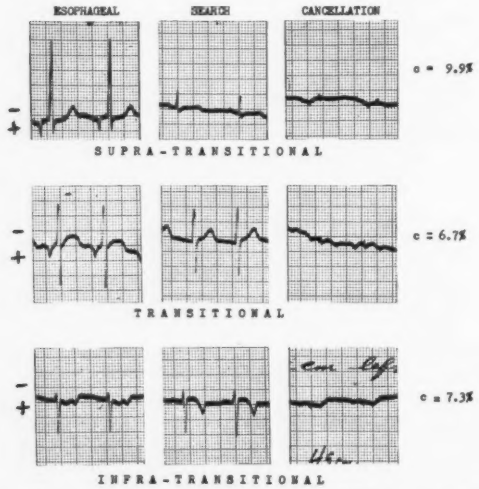


FIG. 1. Typical cancellation of QRS complexes recorded at the supratransitional, transitional, and infratransitional levels of the esophageal lumen. The esophageal tracings were recorded with reversed polarity in order to facilitate recognition of their mirror patterns during exploration of the body surface.

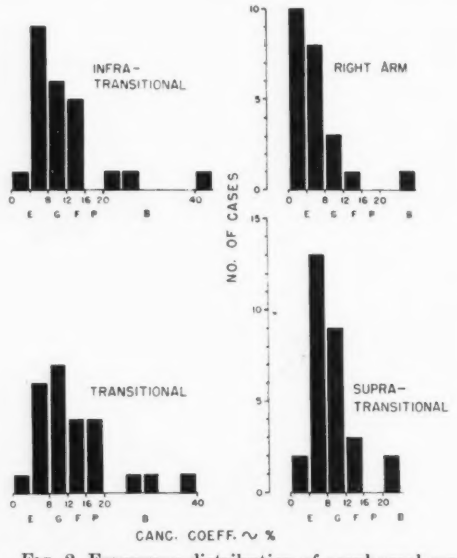


FIG. 2. Frequency distribution of esophageal cancellation data. The data include 24 cancellations at the infratransitional level, 25 at the transitional level, and 29 at the supratransitional level. Twenty-three cancellations of right arm potential were performed to obtain a control value, and to check technic. Schmitt's[1] categories of excellent, good, fair, poor, and bad are indicated by the letters on the abscissas.

TABLE 1.—*Summary of Esophageal Lead Cancellations Performed on Twenty-seven Subjects*

Position	Number of cancellations	Quality of cancellations*					Average cancellation coefficient—per cent	S.D.
		Excell.	Good	Fair	Poor	Bad		
ight arm	23	78.3%	13.1%	4.4%	0%	4.4%	6.1	5.5
ıfratransitional	24	41.7	25.0	20.9	0	8.3	11.2	8.3
ransitional	25	28.0	28.0	16.0	16.0	12.0	13.1	7.9
upratransitional	29	51.8	31.1	10.4	0	6.9	9.3	4.6

* This follows Schmitt's[1] classification of a cancellation coefficient of 0 to 8 per cent as excellent, 8 to 12 per cent as good, 12 to 16 per cent as fair, 16 to 20 per cent as poor, and 20 to 40 per cent as bad. One trial at the infratransitional level resulted in a coefficient of 42.2 per cent, i.e., "no cancellation."

ellation coefficient greater than 40 per cent). This failure occurred at the infratransitional position.

Undoubtedly technical difficulties account to some extent for the fact that cancellation of intra-esophageal potentials were not so good as those of right arm potentials. This seemed to be particularly true at the transitional level, where it was noted that patient discomfort, as manifested by restlessness and swallowing movements, produced obvious changes in the form of the reference electrocardiogram. Schmitt and associates[1] estimated that their cancellation data would have been approximately 20 per cent better if they had searched more exhaustively than practical considerations permitted. In our cancellations of the right arm potentials sufficient care and patience were exercised to achieve virtually optimum results. On the other hand, we probably did not achieve similar precision of esophageal cancellations due to unavoidable movements, especially swallowing, by the subjects. Therefore, it appears likely that cancellations of esophageal QRS complexes exist that are significantly better than our data indicate. However, we do not know how much better such cancellations would be under ideal conditions as compared to practical conditions.

Discussion

Despite the great proximity of the lower esophageal lumen to the heart, surprisingly good cancellation of electrocardiograms derived from this region can be achieved. Such cancellations cannot be explained on the basis of the equivalent cardiac dipole concept because the electrode locations are much too close to the heart to hypothesize that the distribution of electrocardiographic potentials in the vicinity of the esophageal electrode closely resembles the potential distribution due to a single, fixed-location dipole. Therefore, we have developed a new and more general theory of cancellation that includes the cancellation of body surface electrocardiograms as a special case.

The principles of the new theory are illustrated in figures 3 and 4, which show, respectively, the lead field[7, 8] of a "unipolar" esophageal lead connection and of a cancellation network that produces exact cancellation of the esophageal potential at a given instant of the electric cycle of the heart. The fields are plotted as isoflow intervals of lead field current in a 2-dimensional model according to a previously published method.[9] Although the models are highly schematized with respect to shape, electric inhomogeneity, and disposition of the electromotive forces of the heart, the *principles* derived from them apply with complete validity to the cancellation of actual esophageal electrocardiograms.

In the case of the esophageal connection a uniform cardiac dipole front is shown crossing 6 isoflow intervals and thereby producing a relative deflection of 6 units in the recording device. In the case of the cancellation connection the same dipole front extends between 2 flow lines of equal value and therefore produces no deflection of the recording device. Since complete cancellation occurs whenever a dipole front extends between 2 flow lines of equal value in the lead field, it is evident from a con-

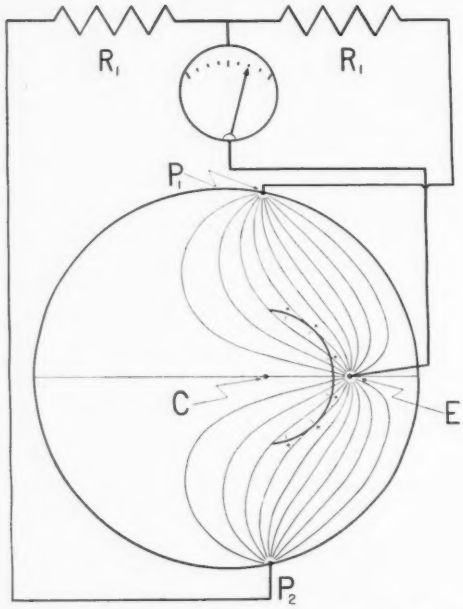


FIG. 3. Lead field (isoflow intervals) of a "unipolar" esophageal lead in a highly schematized, 2-dimensional model of the human body. The reference terminal is formed by connecting the 2 electrodes, P_1 and P_2, together through equal resistors, R_1. Since P_1 and P_2 lie on a vertical axis that passes through C, the reference terminal is indifferent to any dipole that may be located at C. C is also employed as the center of a uniform circular dipole front shown in the figure. The lead field current emanating from the esophageal electrode, E, has been divided into 20 equal portions. Since the dipole front crosses 6 of these isoflow intervals, it produces a relative deflection of 6 units between the terminals of the lead connection.

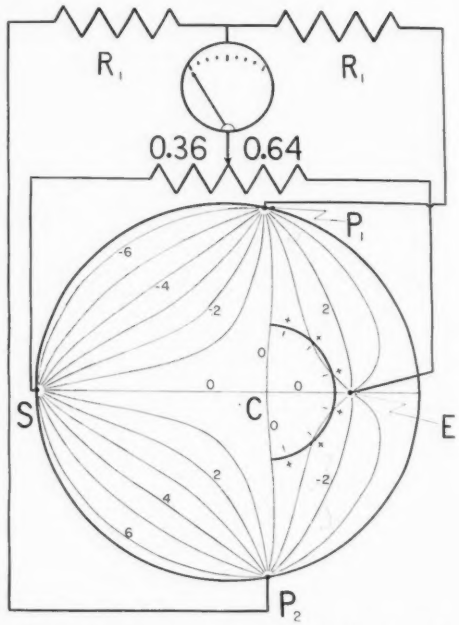


FIG. 4. Lead connection that will produce complete cancellation of the dipole front shown in figure 3. The conditions are the same as in figure 3 except for the addition of a search electrode, S, located on the surface of the model diametrically opposite from the esophageal electrode, E, and a potentiometer connected between electrodes E and S. Adjusting the potentiometer so that 36 per cent of the lead field current enters through E, and 64 per cent through S causes the lines of 0 flow to meet at the center, C, of the circular dipole front. The point, C, is the "electric center" of the cancellation connection, inasmuch as any dipole located at the point will fail to produce a deflection of the meter. Since the circular dipole front extends between 2 flow lines of equal value, it also fails to produce a deflection of the meter. It is evident from a consideration of the lead field that innumerable dipole fronts may exist that will be completely canceled by this particular lead connection. Also note that the lead field in the vicinity of the electric center is much "weaker" than it is in the case of the unipolar esophageal lead connection of figure 3.

sideration of figure 4 that there may exist innumerable dipole fronts about the electric center,* C, which will fail to produce a deflection of the recording device. Conversely, there exist innumerable combinations of search electrode position and potentiometer setting that will produce exact cancellation of the dipole front shown in the illustration.

Because of this infinite multiplicity of cancellation conditions for a single dipole front, at least one such condition can be found that will produce complete cancellation at each of 2 given instants during the electric cycle of the heart. In the case of a diphasic complex the conditions can be arbitrarily chosen to produce complete cancellation of the maximum positive and negative potentials. Therefore, without regard to the equivalent cardiac dipole hypothesis, complete cancellation of the major peaks

* Attention is called to the fact that the electric center is equivalent to the null point of McFee and Johnston.[8]

of a diphasic esophageal QRS complex is assured a priori.

Theoretically, if at all other instants during the QRS cycle the dipole front were fortuitously to extend between flow lines of equal value in the lead field, complete cancellation of the QRS complex would result. In practice the distribution of the electromotive forces of the heart only approximates the ideal distribution, and some potential is usually recorded except at the 2 instants of complete cancellation. However the lead field in the vicinity of the electric center is relatively "weak," and therefore deviations from the theoretically ideal distribution of dipole fronts are minimized in the cancellation electrocardiogram.

This theory of cancellation applies as well to body surface electrocardiograms as it does to juxtacardiac electrocardiograms. For instance, if the esophageal electrode in figure 4 were shifted to a position on the model surface diametrically opposite from the search electrode, and the potentiometer setting then adjusted so that the dipole front again lay between 2 zero-flow lines of the lead field, complete cancellation of the dipole front with respect to a "precordial" electrode would result. The lead field in the vicinity of the electric center would be weaker in the case of the precordial cancellation than in the case of the esophageal cancellation. Therefore, cancellation of the entire QRS complex would tend to be better for precordial electrocardiograms than for esophageal electrocardiograms. This theoretically anticipated difference in the relative excellence of cancellation is in accord with our experimental findings.

The new theory of cancellation presented here resolves the paradoxic implication of the equivalent cardiac dipole hypothesis that proximity electrocardiograms are not strongly influenced by local action currents. As an example, it is apparent in figure 3 that the esophageal electrocardiogram is influenced most strongly by the axial portion of the dipole front. Analysis of the search electrode lead field (not illustrated here) shows that the axial portion of the dipole front exerts the least influence upon the mirror electrocardiogram. Nevertheless, due to the characteristics of the lead field shown in figure 4, exact cancellation does occur. Obliteration of the axial portion of the dipole front, for instance by myocardial infarction, would exert a much stronger influence on the reference electrode than on the search electrode. However, cancellation could readily be re-established by shifting the setting of the potentiometer shown in figure 4.

In comparing the relative merits of the 2 theories of the cancellation phenomenon it should be noted that equivalent cardiac dipole hypothesis is essentially an application of lead vector theory in which it is assumed that the total electromotive activity of the heart can be represented with sufficient accuracy as a single, fixed-location dipole in a homogeneous medium. On the other hand, the new theory of cancellation developed here is an application of the more general lead field theory. The new theory indicates the limitations of the equivalent cardiac dipole hypothesis rather than invalidating it completely, and it does account satisfactorily for the inconsistencies and paradoxes to which the equivalent cardiac dipole hypothesis leads.

Summary

Cancellation of QRS complexes recorded from infratransitional, transitional, and supratransitional electrocardiographic levels of the esophageal lumen was attempted in 27 subjects. Forty-one per cent of the attempts resulted in excellent, 28.2 per cent in good, and 15.4 per cent in fair cancellations.

Because of the extreme proximity of the lower esophageal lumen to the heart, the equivalent cardiac dipole concept cannot be invoked as an explanation for the cancellability of electrocardiograms recorded from this region. A new theory of cancellation is presented that depends upon an analysis of the lead field associated with the cancellation connection.

Cancellation of either esophageal or body surface electrocardiograms is not a critical test of the equivalent cardiac dipole hypothesis because a cancellation connection is a relatively insensitive electrocardiographic lead, and because there is prior assurance that complete cancellation may be obtained at any 2 desired instants of the QRS cycle.

The existence of the cancellation phenomenon does not preclude the possibility that proximity leads are selectively affected by local action currents. On the contrary, it is theoretically certain that proximity leads are affected most strongly by local action currents, despite the existence of cancellation.

Summario in Interlingua

Esseva tentate cancellationes del complexos QRS registrate ab nivellos electrocardiographic infratransitional, transitional, e supratransitional del orificio esophagee in 27 subjectos. Le cancellationes obtenite esseva excellente in 41,0 pro cento del essayos, bon in 28,2 pro cento, e satis bon in 15,4 pro cento.

A causa del extreme proximitate del orificio esophagee inferior al corde, le concepto del equivalente dipolo cardiac non es usabile in explicar le cancellabilitate de electrocardiogrammas registrate ab iste region. Es presentate un nove theoria de cancellation, dependente del analyse del campo de derivation associate con le connexion cancellational.

Le cancellation de electrocardiogrammas ab esophago o superficie corporee non es un test critic del hypothese del equivalente dipolo cardiac, proque un connexion cancellational es un relativemente insensibile derivation electrocardiographic e proque il ha a priori le certitude que cancellation pote esser obtenite a non importa qual 2 instantes del cyclo QRS.

Le existentia del phenomeno de cancellation non exclude le possibilitate que derivationes de proximitate es selectivemente afficite per currentes de action local. Al contrario, il es theoricamente certe que derivationes de proximitate es afficite fortissimemente per currentes de action local, in despecto del existentia de cancellation.

References

[1] Schmitt, O. H., Levine, R. B., Simonson, E., and Dahl, J.: Electrocardiographic mirror pattern studies. I. Am. Heart J. **45:** 416, 1953; II, **45:** 500, 1953; III, **45:** 655, 1953.

[2] Frank, E.: Measurement and significance of cancellation potentials on the human subject. Circulation **11:** 937, 1955.

[3] Seiden, G. E., and Keisman, R. A.: Cancellation of the abnormal QRS complex of heart disease. Am. Heart J. **52:** 62, 1956.

[4] Frank, E.: Absolute quantitative comparison of instantaneous equipotentials on a normal subject with dipole potentials on a homogeneous torso model. Circulation Research **3:** 243, 1955.

[5] —: Determination of the electrical center of ventricular depolarization in the human heart. Am. Heart J. **49:** 670, 1955.

[6] Brody, D. A., Harris, T. R., and Romans, W. E.: A simple method for obtaining esophageal electrocardiograms of good diagnostic quality. Am. Heart J. **50:** 923, 1955.

[7] Lepeschkin, E.: Modern Electrocardiography. Baltimore, Williams and Wilkins Co., 1951, p. 56.

[8] McFee, R., and Johnston, F. D.: Electrocardiographic leads. II. Analysis. Circulation **9:** 255, 1954.

[9] Brody, D. A., and Romans, W. E.: A model which demonstrates the quantitative relationship between the electromotive forces of the heart and the extremity leads. Am. Heart J. **45:** 253, 1953.

Clemedson, C.-J.: Blast Injury. Physiol. Rev. **36:** 336 (July), 1956.

The profound changes of circulation following exposure to a strong shock wave were reviewed. Bradycardia was due essentially to vagal reflexes elicited partly in the damaged lungs, but the cause of lowered arterial pressure in the systemic circulation was not yet established. The available information suggested a number of mechanisms including: reflex hypotension from rupture of the pulmonary capillary bed and reduction in cardiac output brought about by the powerful bradycardia and even by coronary air embolism. Until measurements of cardiac output, coronary blood flow, and pulmonary pressures become available, the definite cause will remain obscure.

Aviado

Idiopathic Myocardial Failure in the Last Trimester of Pregnancy and the Puerperium

By W. R. Meadows, M.D.

Instances of congestive heart failure due to unexplained myocardial disease are not infrequently discussed in the literature. The present study, an extension of a similar study reported by Hull in 1937, relates this type of case to the terminal aspects of pregnancy and the puerperium with an incidence of 1 in 1300 deliveries. Four case reports with necropsy findings, together with the clinical observations made on a total of 15 cases are presented. The frequency of recurrence of the syndrome with subsequent pregnancies and the predominance in the puerperium of this type of congestive failure over those of the usual etiologies suggests that the relationship to pregnancy is not fortuitous.

CONGESTIVE heart failure due to idiopathic myocardial disease appearing for the first time during the terminal aspects of pregnancy or the puerperium apparently was known to earlier writers,[1-5] but it was not until 1937 that adequate clinical and pathologic descriptions appeared in the literature. In that year Hull[6] described the clinical findings in 27 patients, and Gouley, McMillan, and Bellet[7] presented 4 cases with autopsy findings. Since then a number of case reports[8-18] have appeared, and reference to "postpartum heart disease" has been made by others,[19-24] but as yet the syndrome is not generally recognized and is not described in most texts on cardiology.

This communication consists of a report of 4 cases with necropsy findings, the clinical observations made on a total of 15 that, with 1 exception, have been followed for a period of 5 to 9 years since their original hospitalization at Cook County Hospital, Chicago, and a brief comparison with the observations of others. The purpose of this report is to confirm and extend previous observations made on this syndrome and to stress the absence of previous heart disease or hypertension in most of these cases. These instances also add further basis for the belief of previous observers that the coincidental pregnancy is in some way related to the myocardiopathy and suggest that many of these cases may be misdiagnosed as rheumatic or hypertensive heart disease due to the lack of general recognition of the syndrome.

From the Department of Medicine, Cook County Hospital, Chicago, Ill.

Case Reports

Case 1

G. J., a 30-year-old Negro with 10 previous births, entered the hospital on April 18, 1945. Three months after the birth of a female infant on December 10, 1944, she developed paroxysmal nocturnal dyspnea (initially in the absence of exertional dyspnea), occasional precordial pain, frequent emesis, and, later, upper abdominal pain. Physical examination revealed a blood pressure of 150/112, a heart rate of 108, a precordial systolic murmur, P2 louder than A2, but no peripheral signs of congestive failure. The ocular fundi were normal. One week following admission the blood pressure dropped to 116/80, and the heart rate to 88. After 9 days she was discharged much improved.

Five pregnancy records from 1930 to her last in 1949 revealed the finding of a precordial systolic murmur noted during 2 different pregnancies, 1 plus albuminuria in only 1 of 17 tests, and multiple blood pressure readings within normal limits except for occasional diastolic levels as high as 94 toward the end of the last 2 pregnancies.

During the next 2½ years her symptoms and signs persisted, and obvious signs of congestive failure appeared and became severe. Hemoptysis and right pleuritic chest pain were frequent. The diastolic blood pressure was frequently elevated on admission, but readings fell as low as 98/78 during her hospital stays. Gallop rhythm was noted on several admissions. In 1947 she was admitted with generalized anasarca, a pulsating liver, and mild icterus. Following paracentesis and 2 months of hospital bed rest she remained relatively asymptomatic for 2 years during which time the ascites gradually disappeared and pulsation of the liver was no longer detected. Blood pressures ranged between 120/80 and 172/110 during this period, and the systolic murmur and cardiac enlargement persisted. Six weeks after stopping digitalis in June 1949 she began a slowly deteriorating course during which

generalized anasarca, tricuspid insufficiency, and icterus again appeared. Death occurred on June 15, 1951. This patient's hospital diagnoses usually were rheumatic heart disease, less often hypertensive heart disease.

Post Mortem. The heart weighed 525 Gm. All chambers were dilated, especially those of the right side. The myocardium was flabby. The right ventricular wall measured 4 mm.; and the left, 1.3 cm. In the subendocardial layers of all chambers were many yellow or fibrotic areas. A mural thrombus near the apex of the left ventricle overlay a larger area of subendocardial fibrosis. Valvular deformities were absent, and the coronary vessels were patent throughout. Microscopically, degeneration of muscle fibers was seen throughout the myocardium but particularly in the subendocardial and subepicardial zones. The fibers were swollen, pale staining, and vacuolated. Cross striations were indistinct or absent, and golden brown pigment was present at both poles of the nuclei. The interstitium was edematous but showed little cellular infiltration. Small focal areas of fibrosis were scattered throughout the myocardium. The endocardium was somewhat thickened, and in the deeper portion loose cellular granulation tissue extended into the overlying thrombus.

Section of the liver revealed distortion of the lobular architecture, the enlarged central fields frequently being connected by bridges. There was extensive recent and old central necrosis with hemorrhage. Fibrous septa with proliferated ductules frequently replaced the necrotic central and intermediate zones and sometimes reached the portal areas. This process was, in a few places, associated with formation of regenerative nodules, whereas in others the picture of subacute congestion predominated. Other findings were those of a biliary nephrosis, chronic pyelonephritis, and passive congestion of all organs.

Case 2

J. M., a 22-year-old Negro with 3 previous births, entered the hospital on March 14, 1949, complaining of severe left upper quadrant pain radiating into the left flank, which had started suddenly 8 hours earlier. Physical examination revealed a blood pressure of 120/100, a heart rate of 112, and a diffusely tender abdomen with rebound tenderness referred to the left flank. A tentative diagnosis of ruptured ectopic pregnancy was made, but 2 colpocenteses produced only straw-colored fluid. One specimen of urine obtained during the first 48 hours after admission was grossly bloody. On further inquiry a medical consultant found that 3½ months after the birth of a female infant on November 14, 1948, the patient had begun to vomit and soon after had a sensation of substernal fullness, paroxysmal nocturnal dyspnea, exertional dyspnea, and nocturia. He further noted Cheyne-Stokes respirations, a protodiastolic gallop rhythm, an apical systolic murmur, P2 louder than A2, but no peripheral signs of congestive failure.

The record of her last pregnancy revealed multiple blood pressure readings not exceeding 110/80, all urinalyses negative for albumin, and a negative cardiac examination. Delivery records for 1945 and 1947 were similarly negative except for a vague history of treatment for syphilis.

By the fifth hospital day abdominal symptoms had abated, blood pressure had fallen to 94/86, and scleral icterus was temporarily noted. Three blood transfusions had been given during the first 3 days in the hospital. The above symptoms continued to be troublesome, however, and signs and symptoms of advanced congestive failure appeared. Retrograde pyelography on March 24 was negative, and clear urine was seen coming from the left ureter, but she subsequently became febrile and developed pyuria. Several blood cultures were taken and subsequently reported negative. Fundoscopic examination on April 27 was negative. On June 9 the patient complained of tenderness of the left knee and calf muscles, and a positive Homans' sign was elicited. One week later there was an episode of abdominal pain initially in the xiphoid area that later became diffuse. This incident was followed by substernal, left chest and left shoulder pain on June 20. She was discharged August 1.

Six months later she was seen in a debilitated state with generalized anasarca, and she described a recent sudden loss of consciousness. Blood pressure was 100/85 with alternans throughout the complete pulse range, and an electrocardiogram showed a 2:1 atrial flutter that persisted until her death (fig. 1). She reentered the hospital June 1, 1950, and died a day later. A loud precordial systolic murmur heard before her death continued a long standing controversy concerning a diagnosis of rheumatic heart disease on this patient.

Post Mortem. The heart weighed 350 Gm. All chambers were extremely dilated. The right atrium measured 1½ mm. in thickness, the right ventricle 4 mm., and the left ventricular wall from 6 mm. in the apical region to 14 mm. in the basal portion. Mural thrombi were found in the right atrial appendage and in both ventricular chambers adherent to the septal and anterior walls near the apex. In a large area around these adherent thrombi in the left ventricle the endocardium was thickened, light gray, and blended with the underlying myocardial fibrosis to include the inner one fourth of the wall; this endocardial thickening measured 5 cm. in diameter and extended to the lateral wall. There were no valvular deformities, and the coronary arteries were all patent and free of atherosclerosis. Microscopically, many of the muscle bundles were swollen, poorly staining, and contained in paraffin sections small empty vacuoles. Cross striations were

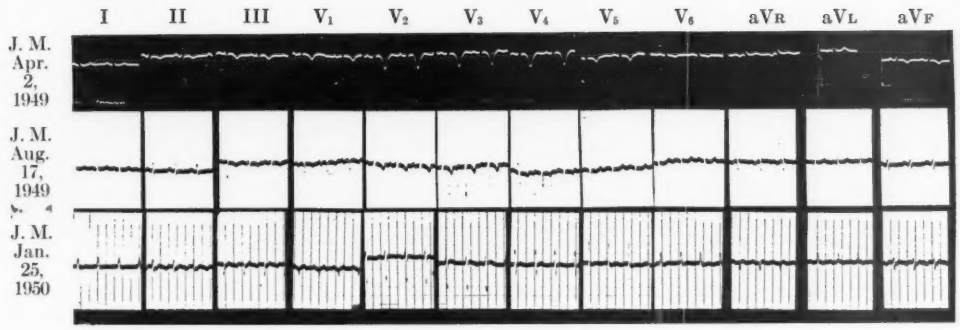


FIG. 1. Electrocardiograms in case 2.

often indistinct and at times could not be made out. The interstitial tissue was edematous. Under the endocardium a few small fibrotic foci were seen, as well as several large foci of eosinophilic necrosis containing small round cells, histiocytes, and pigment-laden macrophages. In other areas the subendocardium was greatly thickened with granulation tissue (fig. 2).

There were multiple hemorrhagic infarcts in the right lung, some dark red and others brown. A large thrombus was found in the right pulmonary artery. Both fibrosing and miliary pulmonary tuberculosis was present with caseous tuberculosis of the tracheobronchial lymph nodes. The kidneys and spleen were also sites of tuberculosis and healed infarcts. The left renal artery was reduced to 2 mm. in diameter, and the left kidney was shrunken as the result of old infarcts. Passive congestion of all organs was noted.

Case 3

D. W., a 29-year-old Negro with 2 previous births, entered the hospital on December 2, 1949. Three months following the delivery of a male infant on September 2, 1949, she experienced an attack of paroxysmal nocturnal dyspnea with hemoptysis, and the third such attack precipitated hospital admission. A cough had been present since the seventh postpartum week. Physical examination revealed a blood pressure of 160/86, a "triple rhythm" with a rate of 115, no murmurs, and A2 equal to P2. Ocular fundi showed grade 1 generalized arteriolar spasm. As objective evidence of congestive failure was not noted, the patient was isolated temporarily because of a suspicion of pulmonary tuberculosis. She was kept at strict bed rest without any specific cardiac medication for 2 months, and symptoms, "triple rhythm," and tachycardia were never noted again. Blood pressure had fallen to 120/80 when discharged. Electrocardiographic abnormalities had disappeared by the time of discharge (fig. 3).

Her obstetrical record revealed blood pressures as high as 190/110 for 3 days prior to her last delivery, with readings of 120/60 on the eighth prepartum day and 136/90 on the ninth postpartum day. Readings as high as 170/100 had been obtained during her first delivery a year previously. No albuminuria or cardiac abnormalities were noted on either occasion.

This patient's blood pressure readings reached hypertensive levels again 1 year later but remained at normotensive levels following radical surgery for a pelvic malignancy in January 1953. She delivered a full-term infant on August 4, 1952, but never experienced further symptoms of cardiac disease. On April 30, 1956, she died from obstructive nephropathy with uremia due to metastatic carcinoma.

A postmortem examination was performed by the coroner. The heart weighed 375 Gm. On section, the myocardium was red-brown in color. The epicardial and endocardial surfaces were not remarkable. A diagnosis of eccentric hypertrophy of the myocardium was made. The remaining findings were those of her neoplastic disease.

Case 4

M. L., a 24-year-old Negro with 3 previous births, entered the hospital on July 28, 1950, with a history of sudden inability to lie flat that had begun about 7 weeks after the delivery of a female infant on April 8, 1950. It was difficult for the patient to describe the sensation that was relieved by sitting up, but at various times she mentioned restlessness, dyspnea, and a substernal oppression radiating through to the back also described as a "smothering pain." Night cough, hemoptysis, exertional dyspnea, and vomiting with occasional hematemesis soon followed. Physical examination revealed a blood pressure of 128/104, a gallop rhythm with a heart rate of 104, and P2 markedly accentuated. No murmurs were noted, and there were no peripheral signs of congestive failure. Eleven days later the blood pressure had fallen to 95/70, and the gallop had disappeared, but she continued to have occasional episodes of vomiting and substernal oppression during the remainder of her 2 months' hos-

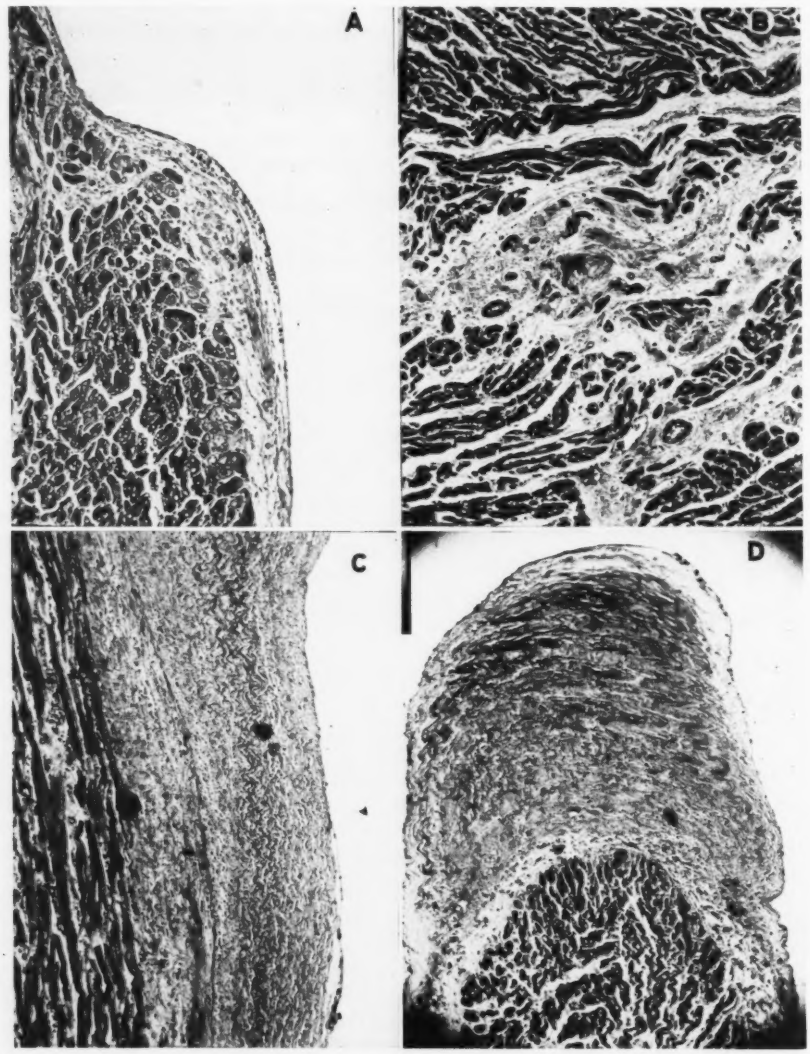


FIG. 2. Microscopic sections of the myocardium of case 2. *A*. Progressive subendocardial fibrosis and zone of vacuolization of subjacent myocardial fibers. *B*. Increase of interstitial fibrous stroma isolating small islands of muscle fibers. *C*. and *D*. Subendocardial thickening due to fibrosis.

pitalization. Recurrent lower abdominal pain and tenderness, which had been noted in the hospital, continued after discharge, but cardiac symptoms disappeared. In the year that followed blood pressures did not exceed 120/80, but gallop rhythm was occasionally heard, cardiac enlargement persisted, and electrocardiograms remained abnormal (fig. 4).

Available records of her 3 pregnancies revealed multiple blood pressure readings not exceeding 124/80, all urinalyses negative for albumin, and a negative cardiac examination on 4 different occasions. The last pregnancy had been eventful only for frequent headaches and abdominal pain.

In the last trimester of this patient's subsequent pregnancy terminating on September 19, 1951, she again developed symptoms and signs of heart failure, which became intractable and resulted in her death on September 8, 1955. During this time she remained for the most part normotensive. It is of interest that in October 1953 an intern in another hospital wrote in response to an inquiry about her: "On each admission there is no agreement as to

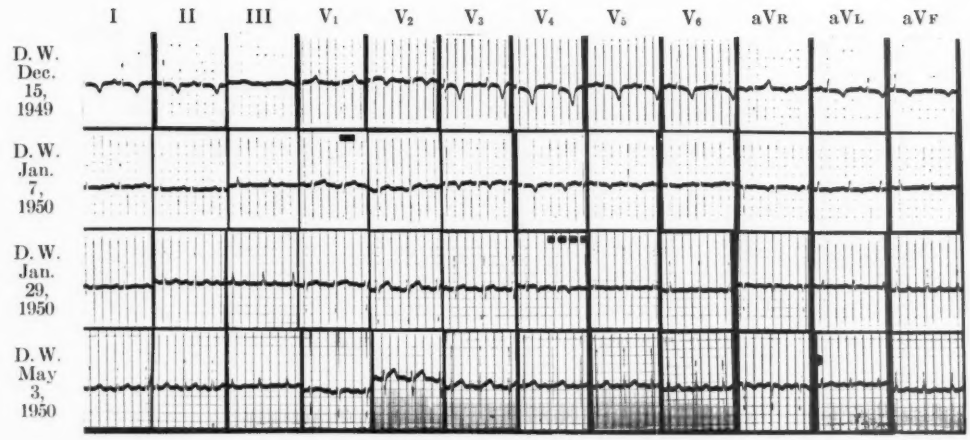


FIG. 3. Electrocardiograms in case 3.

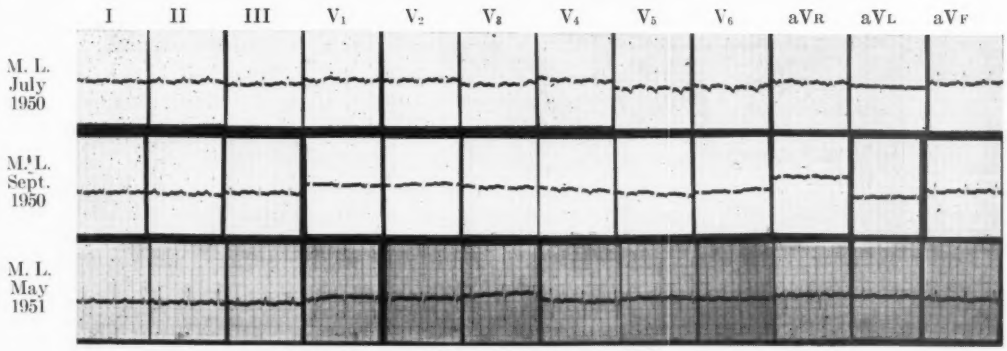


FIG. 4. Electrocardiograms in case 4.

etiology—not even with regard to possible diastolic murmur."

Post Mortem (San Francisco Hospital). The heart weighed 650 Gm. The left ventricle averaged 9 mm. in thickness; the right ventricle, 5 mm. The myocardium was soft, and there was dilatation of all chambers. The endocardium of both ventricles was diffusely thickened. On section of the left ventricular wall scattered areas of fibrosis, yellow-white in color, were found measuring up to 1 cm. in diameter. The endocardium in the left ventricle under the most involved area of myocardial scarring had a large mural thrombus attached that measured 3 by 5 cm. Organizing mural thrombi were also found in the right atrium. The chordae tendineae were slightly thickened, but valvular deformities were absent. The coronary arteries were thin, elastic, and patent throughout their lengths. Microscopically, the myocardial fibers appeared relatively healthy with cross striation visible in most places. A number of fibers were fractured with loose ends apparent and there were a few areas where myocardial fibers were degenerated and showed nuclear changes. The endocardium of both ventricles was markedly thickened with fibrosis and elastic tissue that showed a great infiltration of lymphocytes, plasma cells, macrophages, and a few eosinophils, which involved the superficial layers of the myocardium. A number of myocyte nests were found in the subendocardial region and scattered areas of fibrosis were also seen between the myocardial fibers. Perivascular inflammatory-cell infiltration was noted around the smaller vessels. The epicardium was noted in a few places and was slightly thickened with an indefinite lining (fig. 5).

There was passive congestion of the liver, kidneys, and lungs, and the last 2 organs were the sites of microscopic infarctions. Hydrothorax and abdominal ascites were noted.

Clinical Observations of 15 Cases

Some estimate of the incidence of this syndrome can be made by comparing the total of 6 cases, all of

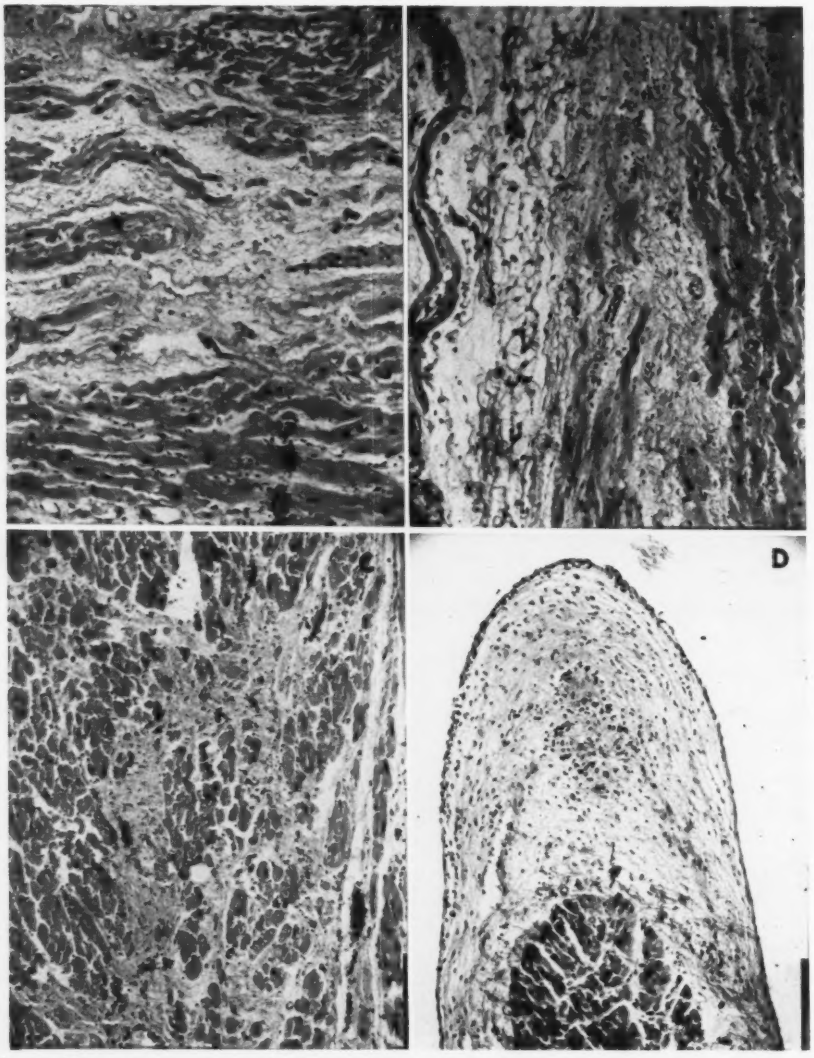


FIG. 5. Microscopic sections of the myocardium of case 4. (*A*) and (*B*) progressive interstitial fibrosis accompanied by round-cell infiltration and loss of myocardial fibers. *C*. Increase of dense interstitial fibrous stroma isolating small islands of muscle fibers. *D*. Subendocardial fibrosis with moderate infiltration of chronic inflammatory-cell elements.

which were Negroes, with the total of 7,519 deliveries that occurred at the Cook County Hospital in 1949. Thirteen of the 15 patients in this series were Negroes. This correlated closely with the proportion of Negro patients on the obstetrical wards but was greater than the 52 per cent given for the total patient population of the hospital. The ages of these patients ranged from 22 to 44 years, and the number of pregnancies from 1 to 10. In 2 instances the last pregnancy had resulted in twin births.

A review of past pregnancy records revealed that a diagnosis of pre-eclamptic toxemia had been made during the terminal aspects of the last pregnancy in 2 instances and that hypertension, i.e., readings exceeding 150 systolic or 90 diastolic, had been a feature of the labor period in 1 other. In no case was hypertension observed to be more than a transient phenomenon. An inconstant systolic murmur had been heard in 3 patients, one of whom eventually was proved to have no valvular lesion at necropsy,

but in no instance was there definite evidence of preexisting organic heart disease.

The past history revealed syphilis in 6 cases and an episode of polyarthritis at age 17 in 1.

Symptoms. The onset of the initial symptoms of congestive heart failure occurred within the first 3½ postpartum months in 11 patients but was as late as 8 months postpartum in 2 and as early as the last trimester of pregnancy in 2. In the latter instances symptoms of congestive failure disappeared at the time of delivery only to reappear again 4 to 8 weeks later. The earliest and most consistent symptoms were cough becoming worse at night and recurrent bouts of paroxysmal nocturnal dyspnea, each symptom being noted by 11 patients. These symptoms usually preceded the onset of exertional dyspnea, orthopnea, and hemoptysis, each of which was noted by 7 patients.

Chest pain noted by 8 patients consisted of recurrent precordial distress in 3 and substernal oppression in 5, 3 of whom had radiation of the pain through to the back. One patient described an associated sensation of numbness in both arms.

Gastrointestinal complaints consisted of nausea and vomiting in 7 and hematemesis in 3. Abdominal pain was reported by 6, and in 1 patient there was postmortem evidence that this had been due to splenic and renal infarction. In 2 instances periumbilical pain had been present since delivery and had preceded the first symptom of postpartum congestive failure by 1 to 2 months.

Cerebral embolism with hemiplegia occurred in 2 patients, and pulmonary embolism occurred in 1 other. These clinical embolic episodes occurred early in the course of the disease, the longest interval following the onset of symptoms being 3½ months. In 2 instances symptoms resulting from systemic embolization were the presenting complaint, and it was only learned later that symptoms of congestive failure had been present for a period of 2 to 5 weeks. Profuse sweating was noted in 2 instances.

In every instance except 1, patients sought hospital admission within 6 weeks of the onset of symptoms.

Physical Findings. At the time of admission to the hospital a labile and predominantly diastolic hypertension was present in every patient except 1. Nine of the 13 patients with diastolic readings between 100 and 116 had systolic readings that did not exceed 150. The remaining 4 had systolic readings between 170 and 190. When this hypertension had appeared in the puerperium was not determined by this study, but in 1 instance it was known to have been present for at least 8 days before the first sign or symptom of the exacerbation of congestive failure that followed a subsequent pregnancy. Pulsus alternans was noted in 3 and later in a total of 6. In 2 instances this sign extended throughout the entire pulse range.

Auscultation of the heart revealed a gallop or "triple" rhythm and a sinus tachycardia in all 15 patients, a precordial systolic murmur of grade I to III intensity in 9, and an accentuated P2 in 12. Cyanosis was prominent in the 2 white patients, and peripheral findings of congestive failure were present in 8.

The ocular fundi were examined in 13 patients and found to be abnormal in 4. This abnormality consisted of narrowing or spasm of the arterioles, with faint cotton-wool-like patches in one and a transient hemorrhage in another.

Laboratory Findings. Albuminuria, present in the 2 patients with a diagnosis of pre-eclamptic toxemia during the last trimester of pregnancy, was found in 11 during the period of their congestive failure postpartum. In only 1 did it fail to clear following cardiac compensation. Hemoglobin values were below 10 Gm. per 100 ml. in 1 case with a hypochromic anemia and a level of 6 Gm. per 100 ml., which was promptly corrected with ferrous sulfate. Persistent neutrophilic leukopenia was noted in 2, but was never explained. Significant eosinophilia was never found. Sedimentation rates were, for the most part, within normal limits. Kahn tests were negative in all cases.

Basal metabolism rates, urea clearance tests, various tests of liver function, total serum protein, serum uric acid, sodium, chloride, phosphorus, cholesterol, and glucose tolerance tests done on a number of patients were within normal limits. Serum potassium determined on 3 patients was initially low in case 4, ranging from 14 to 16.7 mg. per 100 ml. Attempts to demonstrate a virus in the serum of case 3 by animal inoculation proved unsuccessful.

Electrocardiography. Serial electrocardiograms were obtained in 10 patients. The admission electrocardiogram in each instance showed T-wave inversion in multiple limb and precordial leads. In one half the patients this inversion was asymmetric, as is seen in heart strain or digitalis effect, and in the other half the symmetry and depth of the inversion resembled that seen with myocardial infarction. Significant Q waves or conduction defects were not observed at any time, and the only arrhythmia occurred in case 2 many months after onset of the disease.

Tracings were interpreted as being within normal limits from 1 to 7½ months later in 5 patients; although improvement was noted in the graphs of another 4, some degree of abnormality persisted at the time of the last tracing 9 to 19 months later. One was not followed closely, but a normal tracing was obtained 2½ years later.

Roentgenology. Teleroentgenograms of the chest taken upon admission revealed generalized enlargement of the cardiac shadow in all patients. This enlargement was persistent in the 5 who eventually died in congestive failure. In 7 patients the transverse diameter of the heart returned to within normal limits in 3 to 16 weeks, while in another it did not

return to normal until 15 months later. Two patients were not followed closely, but 2½ years later their hearts were found to be within normal limits.

Differential Diagnosis. Three patients who did not have peripheral evidence of congestive failure and in whom the significance of the gallop rhythm was not recognized were given a diagnosis suggested by the most prominent symptom. One admitted with sudden, severe abdominal pain (renal embolus?) was initially considered to have a ruptured ectopic pregnancy; another who had a cerebral embolism subsequently underwent a craniotomy because of the suspicion of a brain tumor; and a third was initially isolated as a case of pulmonary tuberculosis because of the presenting symptom of hemoptysis.

When the congestive failure was recognized, the most frequent etiologic considerations by the staff were rheumatic or hypertensive heart disease. These diagnoses were ruled out on lack of confirmatory evidence in the past hospital records and the evolution of the T-wave changes in the electrocardiogram. One patient with a faint early diastolic murmur at the base and a history of polyarthritis 16 years previously probably had rheumatic heart disease in addition, but the changes in the electrocardiogram were considered to support acute myocardial damage as the cause of the congestive failure. Anemia was an additional etiologic consideration in another, but the cerebral embolism, the absence of murmurs, and the vasoconstriction as reflected by the hypertension were not considered compatible with this sole etiologic diagnosis.

It is apparent from the literature[25, 26] and the experience with these cases that considerable division of opinion as to the nature of the cardiac lesion frequently occurs when this type of case is presented clinically. Not only pericarditis with effusion, but most of the rare causes of heart failure were considered at one time or another in these patients.

Clinical Course. With the exception of case 2, the symptoms of congestive heart failure of all patients were much improved following a period of hospitalization varying from 8 to 60 days. This improvement occurred only in response to digitalization in 1 patient whose severe failure persisted after 26 days of bed rest and treatment with mercurial diuretics and was temporarily interrupted by embolic episodes in 2 others.

Blood pressure readings were repeated on 12 patients before hospital discharge and were found to have fallen markedly in each instance. This fall to normotensive levels occurred within a few days to 3 weeks in 10 patients, but was delayed from 1 to 2 months in the remaining 2, 1 of whom had been toxemic at term. This observation was independent of the status of the congestive failure, the heart size, or the electrocardiogram and could only be correlated with the bed rest the patient was receiving. During the first year following the initial cardiac episode the blood pressures of 5 patients were found to be once again at hypertensive levels. In 3 of the 5 elevated blood pressures were associated with continuing congestive failure and were observed to fall markedly again during periods of bed rest in the hospital. By the end of the fourth year an additional 3 patients were noted to be hypertensive.

The systolic murmur noted in 9 patients on admission diminished in intensity in 2 and totally disappeared in another 2 as compensation was restored and cardiac enlargement decreased. In the other 5, 2 of whom were proved to have no valvular lesion on necropsy, the murmur persisted; and in 2 patients it was not heard until after discharge from the hospital.

A remission of signs and symptoms of heart disease occurred in the 10 patients whose cardiac transverse diameter returned to within normal limits. In 4 this was without any other therapy than 2 to 8 weeks of bed rest, whereas in 1 it occurred many months later without relation to therapy. Except for the exacerbations associated with the subsequent pregnancies of 4 of these 10 patients, 1 of whom has failed to make a complete recovery 5 years later, a complete remission has continued in the 3- to 9-year period that has followed. Four of the 5 patients with persistent cardiomegaly had symptomatic remissions lasting from 9 to 28 months, but all 5 eventually became chronic cardiac invalids and died 1 to 8 years after the onset of symptoms.

Ten patients have had 1 or more subsequent full-term pregnancies, and in 6, 1 of these pregnancies has been associated with an exacerbation resembling the original episode. In 2 instances 2 pregnancies with cardiac involvement either alternated with or were followed by another free of such complication. A further remission has occurred in 3 of the 6, but the 2 patients whose heart size had never returned to normal following the initial episode eventually died in congestive failure.

Comparisons with Previously Reported Cases

With certain exceptions this description is in general agreement with the original given by Hull. He observed the syndrome most frequently in primiparae while in the present series it occurred most frequently in association with the third pregnancy. Seventy-four per cent of his cases as compared with 40 per cent of the present series were symptomatic by the end of the first postpartum month; however, 73 per cent of the present series had become symptomatic by the end of the seventh postpartum week. Generalized anasarca and a small pulse, prominent features of his cases, were usually

ate findings when they occurred in the present series. Hematemesis occurred in 1 of his patients and in 3 of the present series, but has not been reported by other observers. Eventual mortality appeared to be similar in both series.[8]

Chest and abdominal pain were not mentioned in Hull's description but have been reported by a number of subsequent observers.[7, 9, 11, 14, 16, 17] In many instances chest pain has resembled that produced by coronary insufficiency, but it has not always been possible definitely to differentiate it from that due to pulmonary embolism. Sudden severe attacks of abdominal pain have been explained by the necropsy findings of mesenteric thrombosis and splenic and renal infarctions;[7] but chronic, less severe abdominal pain associated with other gastrointestinal symptoms have not received adequate explanation except for the finding of pancreatitis in 1 patient at necropsy.[11] In 1 instance[9] sudden, but transient, excruciating periumbilical pain was the first symptom and preceded the onset of paroxysmal dyspnea by several hours. Chest and abdominal pain have been noted in cases of endocardial fibrosis and idiopathic myocardiopathy unrelated to pregnancy [27-30] and thus are not unique for the type of case under discussion.

Abnormal electrocardiograms, especially shallow T-wave inversion, have been noted by all observers, but the magnitude and evolution of the changes described here are reported for the first time. It seems probable that this discrepancy is a result of the greater number of chest leads taken in recent years.

Hull's series of 27 cases included 2 patients who had had a similar episode following a previous pregnancy and another 2 who had subsequent full-term pregnancies, with 1 again developing congestive failure in the postpartum period. Two of Woolford's[17] 5 cases had subsequent pregnancies, and both again developed congestive failure in the postpartum period. In 1, cardiac involvement followed 3 nonconsecutive pregnancies, the first, third, and fifth.

The only previous observer to report on the frequency of this syndrome was Woolford, who found an incidence of 1 out of every 4,000 obstetrical admissions to the Cincinnati General Hospital.

Pathology

Fifteen necropsies have been reported since 1937.[6-8, 11, 13, 16] With the exception of case 3 these have shown a soft, flabby, and dilated myocardium with ventricular mural thrombi found especially near the apex. Weights have varied from 260 to 650 Gm. with 6 of the 10 reported weights being between 470 and 525 Gm. No significant disease of the coronary arteries has been described, and in only 1 case[7] has a valvular deformity been found. Microscopic features reported include focal and diffuse areas of disintegration of the muscle fibers with occasional hemorrhages, a minimal to moderate cellular response of lymphocytes and macrophages, and myocardial fibrosis; fat droplets in the muscle fibers were an additional finding in 1.[11] These changes have been most intense and diffuse in the subendocardial portion of the myocardium, especially in that portion of the myocardium underlying thrombus formation. Focal endocardial swelling with disruption of the overlying endothelial layer and fibrin deposition as found in 1 early case[7] may be the basis of subsequent thrombus formation as well as the diffuse endocardial thickening found in long-standing cases.[29, 31, 32] It does not appear that these observations differ in any important respect from those found in similar cases unrelated to pregnancy.[29, 33]

Etiology

The cause of the endomyocardial lesions is unknown. Theories as to etiology and pathogenesis of similar lesions unrelated to pregnancy have received consideration elsewhere.[34] In cases associated with pregnancy 2 lines of evidence suggest that the activation of the lesion at that particular time was not fortuitous but occurred as the result of unknown factors operating during and shortly after the preceding pregnancy. These were the frequency of recurrence of the syndrome in relation to a subsequent pregnancy, especially where these pregnancies were not consecutive, and Hull's observation that two thirds of cases of heart failure occurring in the postpartum period were due to heart disease of other than the usual etiologic types.

Two further remarkable features were the

significant increase in the incidence of twin births at the time of the last parturition noted here and by others[6, 9, 17] and the initial acute hypertension associated with the congestive failure. Although the latter has not been an invariable finding, it appears that anything approaching a comparable frequency in similar cases unrelated to pregnancy is to be found only infrequently.[33, 35] The phenomenon of an initially high blood pressure that returns to normal when the congestive failure accompaning hypertension is improved with treatment is not a new observation.[36-39] Unexplained, however, is the constancy of the blood pressure phenomena observed in this series.

While neither the clinical nor the pathologic findings of these cases were those of hypertensive heart disease in the usual sense, several features were suggestive of effects usually attributed to coronary insufficiency. These included the previously described pathologic findings that are compatible with anoxia,[29, 40] the character and radiation of the substernal pain that occurred in at least 5 patients, the configuration and evolution of the T waves in the electrocardiograms, and the results of an oxygen deprivation test in 1 patient. The mechanism of production of such a postulated anoxia is speculative, since minimal vascular changes in cases associated with pregnancy, when described, have been entirely out of relationship to the vast amount of destruction present.[7]

In any consideration of the etiology of cases of this type the question of beriberi or malnutrition almost invariably arises.[41, 42] The lack of definite evidence of dietary deficiency in the history, the absence of any physical stigmata, and the favorable course without vitamin therapy leave little basis for consideration of this etiology in the cases described here. Hull concurred in this opinion and stated that early suspicions that it might represent a nutritional deficiency disease have long since been disproven.[43]

Upper respiratory infections, influenza, and grippe are occasional etiologic considerations when cases of idiopathic myocardial failure occurring in young individuals are reported in the literature, and 3 of these patients did interpret their initial respiratory symptoms as due to "a cold." In the present series of cases it appears that the symptoms of night cough, hemoptysis, and paroxysmal nocturnal dyspnea were the earliest clinical manifestations of myocardial failure rather than its cause.

Marked similarities between this syndrome and the congestive failure produced by desoxycorticosterone suggest that endocrine investigations might be fruitful. Virologic studies are also needed for the further advancement of knowledge concerning these idiopathic disorders of the myocardium.

Treatment

Any consideration of treatment should emphasize that these patients have degenerative heart disease of unknown etiology but that early it is potentially reversible. Thus therapeutic efforts should not rest with the control of the symptoms of congestive failure but should include prolongation of bed rest until after the heart size has returned to within normal limits, when this objective is attainable. While bed rest alone is sufficient treatment in many cases, in others the need for digitalization becomes apparent early. Anticoagulants have not been used in this series. Since embolization, when it occurs, is frequently a very early event in the course of this condition, effective use of these agents would depend on their institution at the earliest possible moment.

Summary

The syndrome of idiopathic myocardial failure occurring in the last trimester of pregnancy or the puerperium is characterized by symptoms of congestive failure, which, early, is predominantly left sided, chest and abdominal pain, embolic phenomenon in 25 to 40 per cent, acute hypertension, gallop rhythm, generalized dilatation of the heart, and T-wave inversion. Pathologic findings, which resemble similar cases unrelated to pregnancy, consist of a soft, flabby, dilated myocardium, ventricular mural thrombi, endocardial thickening of variable extent, and focal and diffuse areas of myocardial necrosis especially in the subendocardial portion of the ventricular wall. Approximately two thirds of the cases make complete clinical recoveries, but the syndrome tends to recur with subsequent

pregnancies. Experience with the present series indicates that these cases are usually considered clinically to have either rheumatic or hypertensive heart disease, one of the rarer recognized forms of myocardial disease, or a disease suggested by symptoms coming from organ embolization.

Acknowledgment

The author wishes to thank Drs. George F. O'Brien, Armand Littman, and John B. Cavenagh of Chicago, George H. Houck of Palo Alto, Calif., and Juan A. Arcellana of Livermore, Calif., for their suggestions in preparing the manuscript. He is also indebted to Dr. Hans Popper of the Cook County Hospital and Dr. John S. Wellington of the San Francisco Hospital for permission to publish the postmortem protocols.

Summario in Interlingua

Le syndrome de idiopathic disfallimento myocardial occurrente durante le trimestre final del pregnantia o durante le puerperio es characterisate per symptomas de disfallimento congestive (que in le phases initial occurre predominantemente al latere sinistre), dolores thoracic e abdominal, phenomenos embolic (occurrente in inter 25 e 40 pro cento del casos), hypertension acute, rhythmo de galopo, dilatation generalisate del corde, e inversion del unda T. Le constatationes pathologic, que resimila casos comparabile sed non connectite con pregnantias, include un molle e flaccide myocardio dilatate, thrombos de pariete ventricular, spissification del endocardio de varie grados, e areas focal e diffuse de necrose myocardial, specialmente in le portion subendocardial del pariete ventricular. Circa duo tertios del patientes effectua un restablimento complete ab le puncto de vista clinic, sed le syndrome tende a recurrer con pregnantias subsequente. Observationes colligite in le presente serie indica que iste casos es generalmente considerate per le clinicos como casos de morbo cardiac rheumatic o hypertensive, de un del formas minus frequente de morbo myocardial, o de un morbo suggerite per symptomas causate per embolisation de organos.

REFERENCES

[1] Virchow, R.: Sitzung der Berliner Geburtshilflicher Gesellschaft, 1870 (Quoted by Porak[2]).

[2] Porak, C.: De l'influence reciproque de la grossesse et des maladies du coeur. Paris, Thesis, 1880.

[3] Blacher, B. F.: A clinical lecture on heart disease in relation to pregnancy and labour. Brit. M.J. **1:** 1225, 1907.

[4] Campbell, D. G.: Pregnancy and heart disease. Canad. M.A.J. **13:** 244, 1923.

[5] Hermann, G. R., and King, E. L.: Cardiovascular disturbances in the obstetric patient. J.A.M.A. **95:** 1472, 1930.

[6] Hull, E., and Hafkesbring, E.: Toxic postpartal heart disease. New Orleans M. & S. J. **89:** 550, 1937.

[7] Gouley, B. A., McMillan, T. M., and Bellet, S.: Idiopathic myocardial degeneration associated with pregnancy and especially the puerperium. Am. J. M. Sc. **194:** 185, 1937.

[8] Hull, E., and Hidden, E.: Postpartal heart failure. Southern M. J. **31:** 265, 1938.

[9] Musser, J. J., Sodeman, W. A., and Turner, R. J.: Heart failure or acute nephritis with onset about 3 weeks after delivery. Ann. Int. Med. **12:** 739, 1938.

[10] —, and —: Heart changes of unusual etiology in pregnancy. Tr. A. Am. Physicians **54:** 181, 1939.

[11] Von Bonsdorff, B.: Severe myocardial failure, acute pancreatitis, and hypocholesterolemia in a young woman shortly postpartum. Acta med. scandinav. **100:** 390, 1939.

[12] Sodeman, W. A.: Cardiac changes in pregnancy unrelated to the usual etiological types of heart disease. Am. Heart J. **19:** 385, 1940.

[13] Vilter, R. W., and McKee, E. E.: Postpartum myocardosis: Case presentation. Ohio M. J. **39:** 142, 1943.

[14] Melvin, J. P., Jr.: Postpartal heart disease. Ann. Int. Med. **27:** 596, 1947.

[15] Freeman, A. M.: Acute postpartal heart failure. J.M.A. Alabama **17:** 163, 1947.

[16] MacKinnon, H. H., and MacKeen, R. A. H.: Postpartum heart disease. Case report. Canad. M.A.J. **61:** 308, 1949.

[17] Woolford, R. M.: Postpartum myocardosis. Ohio M.J. **48:** 924, 1952.

[18] Bashour, F., and Winchell, P.: Postpartal heart disease: A syndrome? Ann. Int. Med. **40:** 803, 1954.

[19] Weiss, S.: Diseases of the heart and the aorta which are not well recognized. M. Clin. North America **23:** 1334, 1939.

[20] Harrison, T. R.: Principles of Internal Medicine. Philadelphia, The Blakiston Company, 1950, p. 1304.

[21] Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J.: Observations on autonomic participation in pulmonary arteriolar resistance in man. J. Clin. Invest. **29:** 1387, 1950.

[22] SAPHIR, O.: Myocarditis. Arch. Path. **32:** 1033, 1941.

[23] JENSEN, J.: Heart disease and pregnancy. Mod. Concepts Cardiovas. Dis. **18:** 31, 1949.

[24] REICH, N. E.: The Uncommon Heart Diseases. Springfield, Ill. Charles C Thomas, 1954, p. 34.

[25] FLYNN, J. E., AND MANN, F. D.: The presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of the thebesian veins in cardiac failure from causes other than myocardial infarction. Am. Heart J. **31:** 757, 1946.

[26] HOFFMAN, F. G., ROSENBAUM, D., AND GENOVESE, P. D.: Fibroplastic endocarditis with eosinophilia: Case report and review of the literature. Ann. Int. Med. **42:** 668, 1955.

[27] LEVY, R. L., AND VON GLAHN, W. C.: Cardiac hypertrophy of unknown cause. Am. Heart J. **28:** 714, 1944.

[28] ROBINSON, R. W., AND QUEEN, R. B.: Isolated (Fiedler's) myocarditis. Ann. Int. Med. **23:** 860, 1945.

[29] BECKER, B. J. P., CHATGIDAKIS, C. G., AND VAN LINGEN, B.: Cardiovascular collagenosis with parietal endocardial thrombosis: Clinicopathologic study of 40 cases. Circulation **7:** 345 1953.

[30] WHITE, P. D., AND FENNELL, R. H., JR.: Endocardial fibroelastosis with marked cardiac enlargement and failure in a man who died at the age of 71 after 15 years of angina pectoris and two years of congestive heart failure. Ann. Int. Med. **41:** 333, 1954.

[31] LENNOX, B.: Acute parietal endocarditis in a case of status asthmaticus. J. Path. & Bact. **60:** 621, 1948.

[32] MCNICOL, M. C., MACMAHON, H. E., BENENSON, A. S., AND WINSHIP, T.: Recurrent parietal thromboendocarditis. Circulation **7:** 497, 1953.

[33] BEDFORD, D. E., AND KONSTAM, G. L. S.: Heart failure of unknown etiology in Africans. Brit. Heart J. **8:** 236, 1946.

[34] WILLIAMS, A. W., BALL, J. D., AND DAVIES, J. N. P.: Endomyocardial fibrosis in Africa. Tr. Roy. Soc. Trop. Med. & Hyg. **48:** 290, 1954.

[35] ELSTER, S. K., HORN, H., AND TUCHMAN, L. R.: Cardiac hypertrophy and insufficiency of unknown etiology. Am. J. Med. **18:** 900, 1955.

[36] FISHBERG, A. M.: Heart Failure. Ed. 2, Philadelphia, Lea and Febiger, 1940, p. 82.

[37] LEVINE, SAMUEL A.: Clinical Heart Disease. Ed. 4, Philadelphia, W. B. Saunders Co., 1951, p. 132.

[38] SCHROEDER, H. A.: Hypertensive Diseases, Philadelphia, Lea and Febiger, 1953, pp. 210, 336.

[39] DAVIES, R. R., MARVEL, R. J., AND GENOVESE, P. D.: Heart disease of unknown etiology. Am. Heart J. **42:** 555, 1951.

[40] GOULD, S. E., ED.: Pathology of the Heart. Springfield, Ill., Charles C Thomas, 1953, pp. 422, 538, 577, 767 and 769.

[41] DOCK, W.: Marked cardiac hypertrophy and mural thrombosis in the ventricles in beriberi heart. Tr. A. Am. Physicians **55:** 61, 1940.

[42] SMITH, J. J., AND FURTH, J.: Fibrosis of the endocardium and the myocardium with mural thrombosis. Arch. Int. Med. **71:** 602, 1943.

[43] HULL, E.: Personal communication.

Heymans, C., de Schaepdryver, A. F., and King, T. O.: Carotid Sinus Baroreceptors and Adrenaline Hypertension. Arch. int. pharmacodyn. **107:** 479 (Sept.), 1956.

These experiments were initiated in response to recent reports by others that baroreceptors are incapable of limiting the blood pressure rise of epinephrine and norepinephrine. The present experiments have shown that the pressor response to a given dose of epinephrine was enhanced after elimination of the buffering activity of the carotid sinus baroreceptors, provided the systemic blood pressure level before and after denervation was kept constant. The well-known function of the carotid sinuses was reemphasized.

AVIADO

SPECIAL ARTICLE

The Evolution of Our Knowledge about the Heart and Its Diseases since 1628

By PAUL D. WHITE, M.D.

IT HAS been a pleasant task to prepare this survey of cardiovascular medical literature since the days of William Harvey, and I am grateful for the opportunity. It seems best to present the review by centuries although there will be, perforce for the sake of continuity, some overlapping. Scattered through the chronologic account there will be included certain general observations about the history of medicine that have been of interest to me during the past 30 years since I first began to pay particular attention to this historical field and since I began to collect many of the noted works about which this article deals.

1600–1700

Italian medicine was at the height of its long reign when William Harvey studied the circulation under the masters of the Padua School in the early years of the seventeenth century. During the next century and a half, and right through the leadership of Morgagni, students and young physicians flocked to that part of the world to begin and to complete their medical studies, particularly in the field of the circulation and its diseases. It is a pleasure to record a pilgrimage that I myself made in 1954 to the ancient medical school in Bologna where an active and stimulating program in teaching and research still continues. This school will be 800 years old in 1958.

The influence and the inspiration of the Italian schools during the middle and later years of the seventeenth century spread widely abroad through students like Harvey in England and his contemporaries in France, in Switzerland, and in the low countries. Oxford, Cambridge, London, Geneva, Basel, Paris, Montpellier, Toulouse, Brussels, Antwerp, Leiden, and Amsterdam all played their roles in the evolution of our knowledge of the heart and its diseases. Through that century and those that have followed it has been evident that no country or race has had a monopoly on science or its practical applications. This seems to be especially true in medicine, where discoveries have been made by the citizens of many nationalities in both the old and the new worlds. Happily no secrets were kept about medical advances which in those earlier centuries were slow for other reasons, namely, the paucity and expense of publication, the lack of adequate transportation, the inhibitive effect of the Inquisition and other tyrannies of the day, and the short lives of the investigators themselves who, like the rest of the population, were exposed to epidemics of plague and other such scourges and to early deaths in battle or at the hands of brigands.

For a century after Harvey it was customary for those writing treatises on the circulation or even chapters in books on medicine to begin the title with the same words that Harvey used, *De Motu Cordis*, no matter what followed. Many of these writings added new observations about the circulation in health and about diseased conditions found at autopsy although in that century there was very little correlation of lesions themselves with symptoms or clinical findings. Cardiology as a special field of practice or teaching had not yet begun. To be sure there were compilations of case records, like that in particular of Theophile Bonet of Geneva, namely the *Sepulchretum* (1679) with its two or three lines of symptomatology and four or five lines of gross autopsy findings, but these were all apparently composed in retrospect by the pathologists who secured the information post mortem

Presented at the Graduation Exercises of the Harvard Medical School, June 1, 1956.

from the family of the victim or from a doctor who had seen him. Despite this fact there are to be found in this remarkable collection of autopsies many "firsts," such as the first recorded sudden death in a middle-aged man with calcareous aortic stenosis, the first case of heart disease interpreted as a cause of severe dyspnea which hitherto had been ascribed to pulmonary disease (but here the lungs were normal), and, in the second edition of the *Sepulchretum* published in 1700, the first rapid death in the case of a man with coronary artery occlusion.

I would hasten to add that even Bonetus, a century before Morgagni, but followed the lead of his predecessors, in particular of the pioneer of case history books Benivieni of Florence who in the year 1507, over 170 years earlier, had published a classic report of 111 cases including several with autopsies. And yet in my own time some writers of medical case histories had thought that they themselves were the pioneers.

It was back in Italy that the final link in the circulation of the blood was discovered. Harvey had assumed that there must be minute connections between the arteries and the veins that are, however, invisible to the naked eye. This assumption was proved to be correct when, in a letter to Borellio, Malpighi in 1661 described the capillaries that he found in the lung of a frog with a magnifying lens. It was van Leeuwenhoek who later in 1688 perfected the microscope itself, a few years before Floyer introduced the pulse watch in 1707. And it was Sir John Floyer who enunciated one of the most important principles of medical practice which should still be applied to all physiologic tests and technics in man (pulse rate, blood pressure level, electrocardiogram, and heart size and shape by x-rays) in the absence of any adequate tables of standards. He wrote:

> It is requisite that every intelligent Patient should thus try his Pulse in a Morning in his Health, that he may inform his Physician what number of Pulses he has in a perfect Health, by which a Physician may judge of his natural Constitution; and the Physician may know how far the diseas'd Pulse receeds from the Natural Numbers; and whether the Numbers of the Pulse are increased or be deficient.

In England after Harvey the names of two leaders in cardiovascular anatomy and physiology stand out. Richard Lower of London published in 1669 his *Tractatus De Corde*, which in clear concise language described in detail the anatomic structure of the heart, showing the heart muscle bands and the coronary circulation. It was he who first described the constricting effect of pericardial disease nearly two centuries before its fuller discussion by Chevers in 1842, and it was he who carried out transfusion in one of the earliest cases, a clergyman with a disturbed mentality, described also by Mr. Pepys at about the time of the plague and great fire in London in 1666. A contemporary case was done in Paris but trouble must have followed in other instances since nothing more was heard about transfusions for over 200 years. Lower added an illustration of his transfusion tubes in his *Tractatus de Corde*.

Another English contributor of note who pioneered in the understanding of the oxygenation of the blood was John Mayow of Oxford, who published his *Tractatus Duo* in 1671 and his *Tractatus Quinque* a few years later (1674). Among the treatises, in addition to that on oxygen (then called nitro-aerious spirit), there was one on the fetal circulation and another on rickets.

Let us go across the channel now to the Netherlands where there lived and worked in Amsterdam a man little known in medical history but, nevertheless, a keen observer. He deserves a prominent place in the Hall of Fame because with one bold stroke of his pen he wiped out about half of all the heart disease of his day. This man was Kerckring who in his *Spicilegium Anatomicum* in 1670 presented his discovery that the so-called polypous disease of the heart was not a disease at all but consisted simply of postmortem clots. In declaring this he apologized to his professors and colleagues for having made this discovery which exposed their universal error.*

---

* There remains, however, in rare cases an exception "that proves Kerckring's rule," namely, a myxoma in the left atrium that can simulate mitral stenosis.

It is fitting, at this time, in closing this brief review of the more important contributions in the cardiovascular field in the seventeenth century, to say a word about priority of medical discoveries and of their publication. Discoveries are, in fact, usually slow processes, credit for them going, as a rule, to the final worker or thinker in the chain of events who adds the finishing touch as Harvey did in 1628. Also many discoveries are rediscovered as in the case of the pulmonary circulation (Ibn Nafis, about 1290, and Servetus, 1553), the explanation of the dyspnea and asthma in mitral stenosis (Vieussens, 1715, and Hope, 1832) the jugular vein engorgement in right heart failure (Lancisi, 1728, and Mackenzie, 1902) cinchona for "obstinate arrhythmia" (Senac, 1749, and Wenckebach, 1914) the description of the tetralogy of Fallot (Sandifort, 1777, and Fallot, 1888), and chronic constrictive pericarditis (Chevers, 1842, and Pick, 1896). As Sir Michael Foster said "To Whom shall be given the honor of a discovery? This question can never be answered fully. Science is a continuous process, each investigator must of necessity build on the work of those who came before him. What we know and what we think is a stream which flows by us and through us, fed by the far-off rivulets of long ago."

1700 to 1800

The eighteenth century saw the beginning of clinical cardiology. The three most important contributors to this new development all published their books in the first half of that century. These volumes are milestones in the development of that high-road and each author deserves special comment.

Raymond Vieussens of Montpellier had already made a notable contribution in the seventeenth century with his *Neurographia* in 1685. Thirty years later in 1715 his more famous treatise on the heart appeared in the vernacular and may justly be considered from the clinical standpoint to be the pioneer work on the subject. Notable was his description of mitral stenosis with the clear recognition of the cause of the dyspnea, which he ascribed correctly to pulmonary congestion secondary to the mechanical effect of the tight mitral stenosis (of which he gives an excellent description) and not to failure of the heart muscle as is even now sometimes wrongly thought, or to disease of the lungs; this concept of Vieussens has been rediscovered in our own day.

A contemporary of Vieussens was Joannis Maria Lancisi of Rome, physician to Pope Clement XI, and a brilliant leader in the medicine of his day. He wrote extensively not only about the heart and its diseases but about other things, medical and non-medical. He was an expert on gardens and on fungi, and he discussed rheumatism and sudden death. In fact his most important contribution was probably the volume *De Subitaneis Mortibus* (On Sudden Death) published in 1707 and dedicated to the Pope. In his book he demonstrated a natural cause for death in every one of a series of individuals who died suddenly in Rome in the winter of 1705 to 1706, proving unfounded the fears of the populace that God in his anger was supernaturally striking down prominent Romans of the day. One of the chief values of the volume is that it demonstrates the scientific interest of the Pope himself in requesting postmortem study, the Church thus urging autopsies for the benefit of our health and understanding. A translation of this book is underway and should help in the struggle against disease. Eight years after Lancisi's death his brother arranged the publication of another important treatise of his concerning the causes and signs of enlargement of the heart and great vessels, *De Aneurysmatibus*. In this book engorgement and pulsation of the jugular veins (Lancisi's sign) were described as evidence of enlargement and failure of the right ventricle almost 200 years before Sir James Mackenzie rediscovered the importance of this phenomenon.

In 1749 the first textbook on heart disease, containing much therapeutic advice, appeared from the hand of Senac, noted Parisian physician of his day and evidently an able cardiologist. He advised opiate and venesection for acute pulmonary edema, rest for heart failure, and quinine for disorders of rhythm. Senac represented the beginning of the revival of the prominence of the French school, especially in cardiology, which reached its height in the

early part of the next century in the persons of Corvisart, Laennec, and Louis.

Also in the first half of the eighteenth century (1733) a classic contribution was made in the field of cardiovascular investigation by Stephen Hales when he published his volume on *Haemastaticks* which contained not only the first direct measurement of blood pressure in a mare but also much detailed analysis of the work of the heart and of the volume of blood. Nearly two centuries passed before sphygmomanometry became a routine clinical procedure and a new generation of physiologic and clinical investigators went further into the field of hemodynamics. Hales was a brilliant star too early for the times.

In the latter half of the eighteenth century there were several very important, though special and almost isolated, cardiological milestones. The first of these came in 1761 when Auenbrugger of Vienna introduced the technic of percussion of the chest to determine in a rough way the heart size and the presence of hydrothorax. This, however, attracted little or no attention, despite a contemporary French translation, until 1808, 47 years later, when Corvisart, Napoleon Buonaparte's physician, called attention to it in a new French translation; Auenbrugger was still alive to receive belatedly due credit for his discovery. Percussion was the first new method of examination to be added in centuries to the brief personal history, palpation of the pulse, and urinoscopy which had been routine through the dark and middle ages ever since the time of Galen.

Also in 1761 appeared the monumental work in gross pathology by Morgagni of Bologna who was 79 years old at the time of its publication. *De Sedibus et Causis Morborum* contained many good descriptions of disease, in particular of heart disease, including the first clear account of the Adams-Stokes syndrome discussed later by Adams in 1827 and by Stokes in 1854.

Then the limelight swung back again to England where a group of able clinicians, some of them close friends, made important discoveries. William Heberden of London in 1768 gave a lecture on angina pectoris, the cause of which he did not know although he recognized it as a serious and dangerous symptom. This lecture was published in 1772, 4 years later. He coined the words describing this symptom in differentiating it from other pain in the chest (dolor pectoris). His friend, Edward Jenner of Berkeley was the one who, in the 1870's, discovered the cause to be obstruction of blood flow due to disease of the coronary arteries which he finally announced in a letter which was published by another associate, Caleb Hillier Parry of Bath in 1799, over 20 years later. Jenner had kept silent all those years because his friend Jonn Hunter had developed angina pectoris and he did not wish to alarm him. Heberden's description of the symptoms was so perfect that it cannot be improved upon today, nearly 200 years later.

Another Englishman, William Withering of Birmingham, an able botanist as well as a good doctor, took advantage in 1775 of the successful use by an old woman of Shropshire of a family recipe for the dropsy and, during the next 10 years, tested the powdered leaves of the purple digitalis in a variety of diseases. In 1785 there was published his *Account of the Foxglove* which, like Heberden's lecture, is one of the great classics in medical literature. He gave exact directions for its use but over 100 years passed before the medical profession appreciated his contribution and followed his advice.

Thus ended a very fruitful century of progress in the evolution of our knowledge about the heart and its diseases.

1800 to 1900

Although there were many more physicians and other scientists interested and working in the field of heart disease during the nineteenth century, their contributions stood out as milestones in a less dramatic way than did those of the eighteenth century, even though, when added together, they were considerable in total volume. There was a steady increase in the clinical recognition of heart disease and in physiologic studies of the circulation, but diagnosis, prognosis, and treatment were still primitive. Certain technics were helpfully introduced for the study of the heart, particularly mediate auscultation with the invention of the mon-

aural stethoscope by Laennec in 1819, the new field of bacteriology that began with Pasteur in the 1860's, and the Roentgen rays in the 1890's.

At first auscultation of the heart was apparently as misleading as it was helpful (witness Oliver Wendell Holmes' *Ballad of the Stethoscope* of the 1840's) but slowly, with the help of Stokes, 1825; C. J. B. Williams, 1828; Austin Flint, 1862; Roger, 1879; and Graham Steell, 1881; the stethoscope became more useful. It was only in the second quarter of the twentieth century that auscultation came into its own through the work of a host of investigators and the introduction of scientific phonocardiography. One especially important auscultatory finding, often of grave significance, gallop rhythm, was first recognized in the nineteenth century (Potain, 1875), but several decades passed before it was rightfully appraised.

Bacteriology came to the fore at the turn of the century and during the first years of the twentieth with the final proof of the syphilitic origin of aortitis and of the majority of thoracic aneurysms (Reuter, 1906), and of the bacterial nature of "malignant endocarditis" (acute and subacute bacterial endocarditis, Schottmüller, 1910). It took a long time, however, before it became clear that a reaction to the hemolytic streptococcus was responsible for much if not all of rheumatic heart disease (Poynton and Paine, 1913, Coombs, 1924, and Coburn, 1931).

Roentgenology, within a few months of its introduction by Roentgen in 1895, was applied to the heart by Williams in 1896. During the next two decades it was rapidly utilized in clinical studies in the two technics of (1) fluoroscopy and orthodiagraphy (Moritz 1902) and (2) teleroentgenography by many workers in the field.

The various kinds of heart disease began to be studied and defined during the nineteenth century. Congenital defects were discussed by Farre in 1814, Gintrac in 1824, Peacock in 1858, Roger in 1879, Fallot in 1888, and Eisenmenger in 1897. Several of their names have remained to designate particular lesions.

Rheumatic heart disease was described by Baillie in 1799, Wells in 1810, Bouillaud in 1840, and many of their successors. Little was said about either hypertensive or coronary heart disease, although Bright (1836) described the big heart found in nephritis and ascribed the enlargement to overwork (as did Allbutt in 1895), and a number of pathologists described coronary artery disease and myocardial infarcts (Parry, 1799; Scarpa, 1804; Hodgson, 1815; Lobstein, 1833; Leyden, 1884; Marie, 1896) and rare cases of clinical coronary thrombosis were described (Hammer, 1878 and Dock, 1896). However, it was necessary to wait until the next century for hypertensive heart diseases to evolve from "cardiorenal or Bright's disease" (although Sir Clifford Allbutt was close to the answer) and for coronary thrombosis to be described clearly as a common clinical entity (Herrick, 1912).

Chronic constrictive pericarditis, long and erroneously called Pick's disease (Pick, 1896), was well described by physicians at Guy's Hospital in London, by Chevers in 1842 and by Sir Samuel Wilks in 1870. It remained for twentieth century physicians and surgeons in the 1920's and 1930's to put it in its proper place.

One other very interesting condition which we now call neurocirculatory asthenia, and which is not heart disease although its multiple cardiovascular symptoms may be confused by the uninitiated with those of heart disease, was described in part by John C. Williams in 1836 but in more detail by B. R. Myers in 1870 and Da Costa in 1871. Its etiology still remains obscure in 1957.

Arrhythmias attracted more attention during the nineteenth century although they had actually been noted in all their forms ever since Galen described them in detail in the second century A.D. However, labels began to be attached to them, for example, paroxysmal tachycardia by Bristowe in 1887 and Bouveret in 1889. Changes in the pulse volume were also defined, such as pulsus alternans by Traube in 1892, and the so-called paradoxical pulse by Kussmaul in 1873. Towards the end of the century these various abnormalities of the pulse were brought together by Mackenzie and Wenckebach whose clinical observations, based on arteriograms and phlebograms, culminated in their notable contributions in 1902 and 1903

respectively; but atrial fibrillation was still to be described in 1909, independently, by Thomas Lewis, and Rothberger and Winterberg, and atrial flutter by Ritchie in 1911. Ventricular fibrillation, however, had been identified in the experimental animal as long ago as 1850 (Hoffa and Ludwig) and 1887 (McWilliam). Heart block with very slow or intermittent pulse had been clinically known and defined much earlier, as already noted, and described in laboratory animals by Stannius in 1852 and by Gaskell in 1881. Kent and His described their so-called bundles in 1891 and 1893 respectively.

During the latter half of the century, the electric activity of the heart was being studied in laboratory animals and in man (Kölliker and Müller, 1855; Sanderson and Page, 1878; Waller, 1887; Bayliss and Starling, 1893), but it was not until Einthoven invented the "string galvanometer" in 1903 that clinical electrocardiography became possible.

Other physiologic technics that were developed during the latter half of the century included vital capacity recording (Hutchinson, 1846), sphygmography (Vierordt, 1855, and Marey, 1860), ballistocardiography (Gordon, 1877), blood flow studies (Pick, 1870, and Stewart, 1894), and sphygmomanometry (Von Bausch, 1881, and Riva Rocci, 1891), but all these studies were in their early stages and became clinically applicable only in the next century.

Finally, although during the nineteenth century treatment of cardiovascular disease began to develop slowly, it was still in a primitive stage in 1900. The remedies described by Senac in 1749 were still largely operative—rest, which was often effective, venesection, which on occasion was helpful in acute pulmonary edema but which was largely overdone until the latter part of the century, leeches, a light diet (though there were no clear rules about salt or fat except that the Karell diet (1866) consisting of 200 ml. of milk 4 times a day did have a low content of salt and fluid as well as of calories and, for short intervals, is still quite effective in the treatment of congestive heart failure), opiates in emergency, mercury in toxic doses such as the Massachusetts General Hospital doctors were still using for rheumatic fever in the 1840's, and foxglove, usually in improper dosage and in the wrong cases. A purified form of digitalis scientifically designated digitoxin but called digitaline was introduced in France by Nativelle in 1845. Lauder Brunton recommended amyl nitrite in preference to spirit for angina pectoris in 1867, and Murrell introduced nitroglycerin in 1879. Pericardial paracentesis was begun by Vernay in 1856 and in 1898 Delorme recommended pericardial resection for chronic constrictive pericarditis, no one, however, following his advice for a good many years (Sauerbruch, 1913, Rehn, 1920, Schmieden, 1924, Churchill, 1929, Beck, 1930). Southey introduced his "tubes" in 1877 and, even now, they prove helpful on occasion. Farina and Rehn in 1896 began to operate on the heart to repair wounds.

And so the century closed with very many minor advances which, however, when added together assumed a considerable total; but there was still, in general, a lack of team work between internists on the one hand and physiologists, pathologists, and surgeons on the other.

1900–1957

Before presenting certain outstanding specific advances in the first half of the twentieth century, I would like to review a few of the general reasons for the remarkable development of our knowledge of diseases of the heart and blood vessels during the last generation.

Until after the first world war, that is, about 1920, there was little or no recognition of the wisdom of specialization in the field of internal medicine. Even today in certain parts of the world, including areas in the U.S.A., there is in practice, teaching, and research a reluctance to subdivide the body. Yet, to many of us, it was quite obvious several decades ago that such specialization and concentration in practice must develop in order to advance our knowledge. It was our thought then, and it still is, that groups of people specializing in different fields can, by their propinquity and frequent consultations with each other, keep their feet on the ground and maintain a proper

point of view. This must be true also of our special community health drives. Until we have progressed further than we have to date we are not in a position to relax and, as frequently is said, to put the body back together again in perfect order. Eventually, after we have mastered the main health problems that still face us then we can probably get along with one community drive and one hearing before the Committees in Congress.

Thus, specialization beginning about 1920 has, without doubt, been largely responsible for the fact that more has been learned about the diagnosis, prognosis, and treatment of diseases of the heart and blood vessels in the last generation than in all the centuries before.

The second important reason why such an advance has taken place in our knowledge, not only of heart disease but also of almost all other fields in medicine, is the development of team work, both between the various workers in the basic sciences and those in the medical and surgical fields in the community, and also through the coordination of such activities by national and international teams. Cooperative researches have been, and will continue to be, very valuable. One of the needs of the future is that of international epidemiologic cardiovascular research to study the relationship of the ways of life to heart disease throughout the world.

The third reason for the great advance in this generation is that heart disease has been accepted as a major public health problem just as, in the past, infections like tuberculosis, poliomyelitis, and the various kinds of cancer had been accepted. This acceptance has resulted in the support of research through private and public funds, highlighted by two events, the establishment of the American Heart Association in 1924 and its recognition some 20 years later of its role in cardiovascular research, teaching, and community programs, and the establishment of the National Heart Institute and National Advisory Heart Council under the wing of the U. S. Public Health Service, by act of Congress in 1948. At the hearings before the House and Senate Committees every year there has been afforded an opportunity to educate the legislators and, through them, the public at large, to the need for research and training in heart disease.

Now as to certain major specific advances, in 1912 James Herrick of Chicago published a paper in the Journal of the American Medical Association that will remain a medical classic for all time. It was entitled Clinical Features of Sudden Obstruction of the Coronary Arteries. This was the basis on which rests our growing knowledge of this major threat to the health of our young and middle aged males in this country today. A very important and useful related study by Schlesinger and Blumgart in 1937 concerning the development of the collateral coronary circulation has explained the role of nature in the common experience of recovery from coronary insufficiency without either wonder drugs (except the very useful role of nitroglycerin) or surgical technics.

The second major milestone in our knowledge of heart disease came in the form of a paper by Richard Cabot published also in the Journal of the American Medical Association, two years later, in 1914, entitled The Four Common Types of Heart Disease: an Analysis of 600 Cases. This directed attention to the etiologic factors in contrast to structural defects and functional disorders which are, of course, also important, but should be preceded in the diagnosis by the etiologic factor. Following this paper of Richard Cabot's there developed, slowly, in various centers, the recognition of the importance of this change in the classification of cardiac diagnosis. The earliest paper in this field was that by White and Myers in 1921 entitled The Classification of Cardiac Diagnosis.

The third great specific advance has been that in cardiovascular surgery to which I have already referred. First the outside of the heart was worked on when a constricting pericardium was removed successfully. Then other surgery on the blood vessels around the heart developed, for example, the ligation and section of the congenitally patent ductus arteriosus (Gross, 1939), by anastomoses carried out by Blalock and Taussig (1945) and by Potts (1946) for the tetralogy of Fallot. Later, there developed the surgical correction of coarctation of the aorta (Gross, 1945, Crafoord, 1945).

Finally, the interior of the heart now has become subject to correction. Although an effort was made by Cutler in 1924 to correct the lesion of tight mitral stenosis, inadequate technic and anesthesia of the day forced a delay of some 20 years until after the second world war when several courageous surgeons (in particular Harken and Bailey) initiated the successful surgical amelioration of the effects of mitral stenosis.

Medical advances too have been of great significance. A number of congenital cardiovascular defects, not even recognized clinically a generation ago, such as coarctation of the aorta, are now easily diagnosed. The importance of correct diagnoses in congenital defects is clearly borne out by the possibility of surgical cure or improvement. In the diagnosis of these defects and also in the case of rheumatic valvular disease (in particular mitral stenosis) and for chronic constrictive pericarditis, cardiac catheterization has been of the greatest value. This was first done by Forssmann (who received a Nobel Prize in 1956) on himself in 1929 and was developed as a practical routine measure by Cournand and Richards in the years that have followed (they also received Nobel Prizes in 1956). Advances in the field of electrocardiography have also been outstanding due, particularly, to the introduction of chest leads in practice by Wood and Wolferth in 1932. Now vectorcardiography is beginning to be introduced in a useful way, although there is much still to be done in its appraisal and final establishment. Similarly, ballistocardiography is going through the pains of childbirth.

Medical treatment of heart disease has developed since 1900 so rapidly that those of us who were taught in medical school in the first two decades of the century had very little idea of what to do for cardiac patients. The proper use of digitalis, the use of quinidine sulfate for the control of arrhythmias, the introduction of mercurial diuretics in a practical way (Saxl, 1920), the introduction of the low sodium diet for congestive heart failure (Widal and Lemierre, 1903, Schroeder, 1941), and the use of the antibiotics in the control of infectious causes of heart disease have all made the difference between our hopeless therapy of years ago and the optimism that is rightfully ours today.

Our knowledge of the prognosis of heart disease has also made great strides in the past generation because some of the conditions, such as myocardial infarction, were just beginning to be recognized 30 years ago and a long follow-up has been needed to determine more adequately the prospects of those who are affected by myocardial infarction due to coronary thrombosis. A much neglected area in prognosis is that of the recognition of the importance of heredity and the taking of an adequate family history.

May I add that one of our defects today, both of commission and omission, is to attempt to provide an answer concerning all the aspects of the medical problems that beset us in diagnosis, prognosis, treatment, and prevention, by setting up programs across the board, that is, one standard for all. We know from our clinical experience in the practice of medicine that in diagnosis, prognosis, and treatment, the individual and his background of heredity are just as important, if not more so, as the disease itself. Far too little attention has been paid to research on the host, i.e., on human genetics, while much study has been done and is projected for the future on the agent, that is, on the effect of the various ways of life. It is timely that we should begin concentrated efforts to determine the candidates for whose sake we should apply in particular the preventive measures that we may discover in the future.

Two of the greatest problems remaining for us to take up with vigor are rehabilitation of cardiovascular patients and epidemiologic cardiovascular research, that is, the relationship of the various ways of life to disease of the heart and blood vessels. This last is the basis for our ultimate aim in preventive medicine. Until we learn all the answers, however, may I suggest that more attention be paid to the simple rules of health such as were advanced and often applied by our medical ancestors of centuries ago. These, if adequately carried out, especially by candidates for certain diseases such as hypertension and coronary atherosclerosis, might, for all we know, prevent or delay the onset of these diseases. At least we must try to find out if our diet is too rich and if our life is too soft. There may be more truth than poetry in such a statement, howbeit an

exaggerated one, as that made by John Dryden in 1680 in a letter to a kinsman:

"By chase our long-liv'd fathers earn'd their food;
Toil strung the nerves and purified the blood;
But we, their sons, a pamper'd race of men,
Are dwindled down to three score years and ten.
Better to hunt in fields for health unbought
Than fee the doctor for a nauseous draught.
The wise for cure on exercise depend;
God never made his work for man to mend."

But lest we become overconfident in our accomplishments let us remember the advice of the old man in Adelphi, the comedy of Terence, quoted by William Harvey:

For never yet hath anyone attained
To such perfection, but that time and place,
And use, have brought addition to his knowledge;
Or made correction, or admonished him,
That he was ignorant of much which he
Had thought he knew; or led him to reject
What he had once esteemed of highest price.

Most learned Riolan, by the help of the Presse, many years ago, I published a part of my labour: But since the birth-day of the Circulation of the Blood, almost no day has past, nor the least space of time, in which I have not heard both good and evill of the Circulation of the Blood which I found out: Others rail at it, as a tender babie unworthy to come to light; Others say, that it's worthy to be foster'd, and favour my writings, and defend them; Some with great disdain oppose them; Some with mighty applause protect them; Others say, that I have abundantly by many experiments, observations, and ocular testimony, confirm'd the Circulation of the blood against all strength and force of arguments; Others think it not yet sufficiently illustrated, and vindicated from objections; But there are who cry out, that I have affected a vain commendation in dissection of living creatures, and do with childish slighting dispraise and deride at Frogs and Serpents, Gnats, and other more inconsiderable creatures brought upon the Stage, and refrain not from ill language. But I think it a thing unworthy of a Philosopher and a searcher of the truth, to return bad words for bad words; and I think I shall doe better and more advised, if with the light of true and evident observations, I shall wipe away those symptomes of incivility.

It cannot be eschewed but doggs will bark and belch up their surfeits; nor can it be help'd but that the Cynicks will be amongst the number of the Philosophers; but we must take a speciall care that they do not bite, nor infect us with their cruel madnesse, or lest they should with their doggs teeth gnaw the very bones of principles of truth.—WILLIAM HARVEY, *De Circulatione Sanguinis*, 1649.

CLINICAL PROGRESS

Selection of Patients for Mitral and Aortic Valvuloplasty

By LAURENCE B. ELLIS, M.D., WALTER H. ABELMANN, M.D., AND DWIGHT E. HARKEN, M.D.

THE operation to correct mitral stenosis has proved its value in the past 8 years. Aortic stenosis can also be palliated surgically but the results are less dramatic, the risk is higher, and the pathologic process often limits the quality of the repair. Operations for mitral and aortic insufficiency are still in the experimental stage, but are improving. This article is concerned chiefly with the selection of patients with predominant mitral stenosis for operation. Such an operation has been termed by us "valvuloplasty." Operations with similar objectives, i.e., fracturing and cutting fused commissures, separating fusion of the chordae tendineae, and withall returning the maximum valvular action to the stenotic complex have been variously designated as "commissurotomy," "valvulotomy," or "valvotomy."

Physicians treating patients with rheumatic mitral valve disease are now faced with the question whether or not to recommend operation. In making such a decision several factors are involved. As in any condition where there are alternative medical and surgical treatments, the decision requires knowledge of the specific medical prognosis, the operative risk, and the results to be gained from surgery.

MITRAL STENOSIS

Summary of Present Indications for Operation in Predominant Mitral Stenosis

Our opinion as to which patients should be offered operation has not changed since our early experience. The results of surgery have borne out our original concepts and these have now been generally accepted.[1-4] Patients with the murmur of mitral stenosis but without symptoms (group I) do not need operation. Many of them remain asymptomatic for many years. It must be remembered that the operation for mitral stenosis is a good palliative but not a curative operation, although the palliation is often life-saving. In patients with moderate but nonprogressive symptoms (group II), the operation may be considered elective. The decision depends on the patient's social, economic, and psychologic situation. The patients in this as well as in other groups should be observed with care and given medical treatment when possible before advising surgery. Frequently, with simple medical measures and readjustment of the patient's life the symptoms become remarkably ameliorated. Some unusual situation such as pregnancy or severe infection may have precipitated cardiac symptoms. Without such stress the patient may enjoy a good state of compensation.

Patients in group III, disabled by progressive symptoms, chiefly dyspnea, but who have not yet become complete cardiac invalids or progressed to chronic persistent congestive failure, need the operation *urgently*. The risk at the present time is very low and the results are excellent. The medical prognosis of these people is poor.

Group IV patients are cardiac invalids condemned to a life of complete inactivity under medical treatment, with a relatively short life expectancy. Although the operative risk in these patients remains high, the results are surprisingly good and operation should be offered. Physicians should be alert, however, to urge operation while these patients are still in group III when much can be accomplished at a low operative risk. It is bad practice to wait

From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, the Surgical Service of the Peter Bent Brigham Hospital, and the Departments of Medicine and Surgery, Harvard Medical School.

This investigation was aided by a grant from The National Heart Institute (H 442).

until they have slipped into group IV. While the results of surgery contrast brilliantly with medical therapy in this category, we must not let this *conceal the great disservice that has been done the patient by allowing him to move from group III into IV*. The operative risk to the patient has increased perhaps 30 times and his potentialities for rehabilitation have diminished.

Operative and Postoperative Prognosis of Mitral Stenosis

Our conclusions as to the value of the procedure are based on a study of 1,000 consecutive patients operated upon for predominant mitral stenosis by one of us (D. E. H.).

Many of the patients in this group were diagnosed preoperatively as having some degree of mitral insufficiency in addition to the stenosis. Patients with minor degrees of aortic valve disease and with tricuspid incompetence were included. We have previously reported a follow-up study of the first 500 of these patients[1] and the more recent data bear out the conclusions reached at that time.

No patients in group I have been operated upon. There have been only 19 in group II, and these have been included in group III for statistical purposes. Group III patients constituted nearly three fourths of the entire group and the remainder were group IV patients.

The mortality of mitral valvuloplasty in the first consecutive 1,000 has steadily fallen, so that the risk in group II and group III patients is now less than 1 per cent. There were but 2 deaths among the group III patients in the last 500 of this series. However, the group IV mortality remains high at about 20 per cent. This emphasizes the importance of operating on patients before they slip from group III to group IV. This deterioration can usually be anticipated.

Seventy-eight per cent of the patients in group III and 62 per cent of patients in group IV showed significant postoperative improvement at the time of the most recent follow-up report. Criteria for improvement have been defined elsewhere.[1] The degree of improvement in group III patients has been maintained over a follow-up time up to 5 years (fig. 1). Thus the

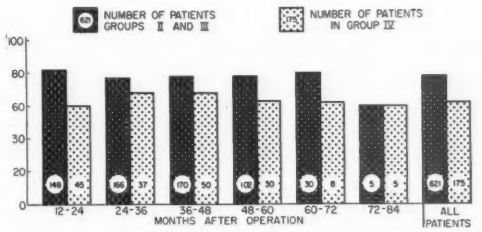


FIG. 1. Per cent of improvement in patients followed one or more years after operation for mitral stenosis.

improvement from operation is persistent, and the number of significant regressions is small. The same is true for group IV patients. The degree of improvement in group III patients after 6 or more years is less than for the first years but the differences are not significant because of the small number of patients followed.

Some skeptics argue that improvement may be due to the psychologic effect of the procedure or to better medical care and not to the operation itself. We have data, as have others, indicating that the hemodynamics of the circulation actually improve after the operation in a considerable number of patients. This long-term clinical study of a large number of patients constitutes further evidence. The simple fact that the good results persist suggests that the operation has fundamentally altered the patient's course. The ultimate test of the value of this operation, of course, will be whether these patients will survive longer than comparable patients treated medically.

Prognosis of Patients with Mitral Stenosis Treated Medically

It is almost impossible to obtain data on medically treated patients similar to this surgical series of 1,000. Most studies are either statistically invalid or the groups not easily comparable. Some studies based on autopsy statistics are retrospective, so that it is almost impossible to determine when and to what degree the patients became symptomatic. Grant[5] reported a group of soldiers with rheumatic heart disease followed 10 years after World War I. This important study dealt with young males only. He found that 45 per cent of

the patients who originally had poor exercise tolerance were dead at the end of 10 years, and all were dead who had shown congestive symptoms.

A study by Wilson and Greenwood[6] on life expectancy, which is not strictly comparable with ours, indicates that about 50 per cent of their patients who originally had shown severe pulmonary congestion or atrial fibrillation were dead in 5 years, and 60 per cent of those who at any time had shown right heart failure were dead at this point. Hamilton and Thomson[7] cited statistics on women in the child-bearing age to the effect that 20 per cent of the "favorable" and 63 per cent of the "unfavorable" cardiac patients were dead after 10 years. Most of their "favorable" patients would belong in class 1 and 2 in the American Heart Association or our classifications. Most of the "unfavorable" group would fall in our groups III and IV.

The only series comparable to ours of which we are aware is that by Olesen,[8] who studied a group of medically treated patients first observed between the years of 1933 and 1949 in Copenhagen. One hundred seventy-six of these patients were classified according to the American Heart Association in class 3 or were fibrillating patients in class 2, and 52 were in class 4. These are comparable to our groups III and IV. The average age and the sex distributions are almost exactly the same as in our patients. What then are the results in our series of operated patients as compared with Olesen's medically treated patients, so far as survival is concerned? Figure 2 shows the results in group III patients over a 7-year period. Of the medically treated patients, 51 per cent survived for 7 years. Of the surgically treated patients the survival rate was 87 per cent after 7 years including an operative mortality of 3 per cent. Thus the survival rate in the operated patients was significantly better than in Olesen's group of medically treated patients. One must bear in mind, of course, that many of these medically treated patients were observed prior to some of the more recent advances in cardiac therapeutics and, in particular, before the advent of antibiotic treatment.

The group IV patients have been similarly compared and gave even more striking results (fig. 3). In our group of operated patients survival rate has been 54 per cent at the end of 7 years, including the mitral operative mortality of 24 per cent. Only 6 per cent of Olesen's medically treated patients were alive at the end of 6 years. In comparing the 2 groups, the operated patients are still better off as far as survival is concerned even at the end of the first year of observation, which includes the operative mortality. The difference between the survival of operated and medically treated patients is so striking in both groups III and IV that it is evident that the operation for mitral stenosis has increased life expectancy. Moreover, the operated patients have, for the most part, lived lives of much greater comfort and usefulness, in contrast to the deterioration that characterizes the patients under medical treatment.

Preoperative Evaluation of the Patient with Mitral Valvular Disease

The preceding discussion has been concerned with over-all results of a large group of patients who were diagnosed preoperatively as having

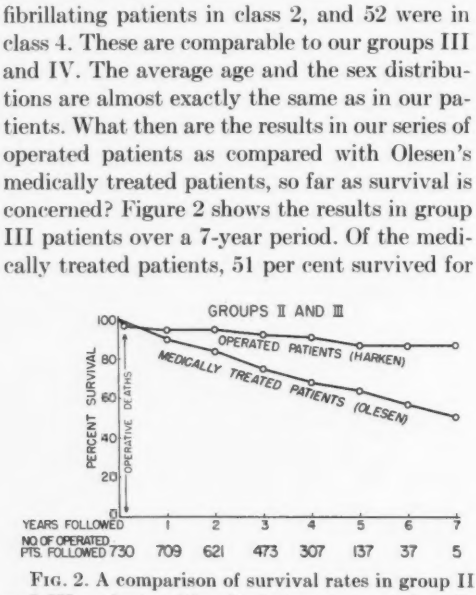

GROUPS II AND III
PERCENT SURVIVAL
OPERATIVE DEATHS
OPERATED PATIENTS (HARKEN)
MEDICALLY TREATED PATIENTS (OLESEN)
YEARS FOLLOWED
NO. OF OPERATED PTS. FOLLOWED 730 709 621 473 307 137 37 5

FIG. 2. A comparison of survival rates in group II and III patients with mitral stenosis treated medically and surgically.

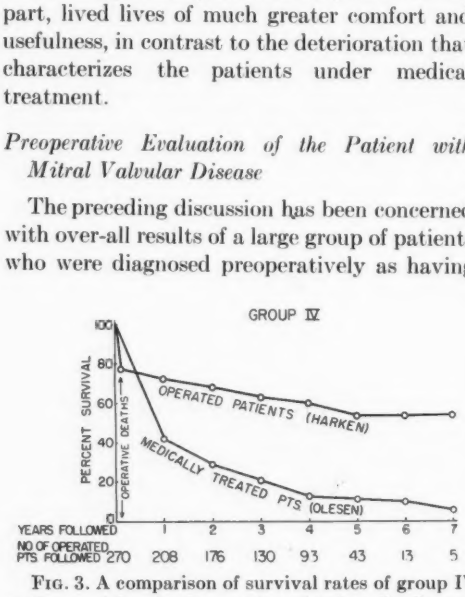

GROUP IV
PERCENT SURVIVAL
OPERATIVE DEATHS
OPERATED PATIENTS (HARKEN)
MEDICALLY TREATED PTS. (OLESEN)
YEARS FOLLOWED
NO. OF OPERATED PTS. FOLLOWED 270 208 176 130 93 43 13 5

FIG. 3. A comparison of survival rates of group IV patients with mitral stenosis treated medically and surgically.

predominant mitral stenosis. When individual patients are under consideration for operation, the degree of mitral stenosis and the extent to which the symptoms are attributable to obstruction at the mitral valve or to other factors must be assessed.

Degree of Stenosis

Insistence that symptoms be present and either disabling or progressive before considering mitral valvuloplasty has proved to be a good method of limiting surgery to patients with hemodynamically significant stenosis. It allows those with only "auscultatory" stenosis to avoid surgery. Although an occasional asymptomatic patient with severe stenosis changes to a rapid deteriorating course, the symptomatic stage of mitral stenosis is generally of gradual onset and there is ample clinical warning before life is threatened and operative risk is significantly increased.

There are patients whose symptoms are atypical or whose history is difficult to interpret. These include patients who tend to minimize symptoms and conceal disability. They often adjust their lives remarkably to their limited capacity. Conversely, there are patients unusually aware of symptoms. This group includes patients with cardiac neurosis or neurocirculatory asthenia. Careful history from family and friends and prolonged observation of the patient may help in clinical assessment. Right ventricular hypertrophy by electrocardiogram or enlargement of the right ventricle and pulmonary artery by fluoroscopy suggests significant stenosis. Often a valid clinical decision can only be made by means of objective tests of cardiac function, e.g., cardiac catheterization, or over-all cardiopulmonary performance, as suggested by Bruce.[9] If the lesion is pure mitral stenosis and no other cardiac or pulmonary disease is likely, direct evidence of pulmonary hypertension and elevated pulmonary wedge ("capillary") pressure, especially during exercise, constitute adequate indications for operation. This is one group of patients in which catheterization of the right heart may still be of clinical value.

When, however, the clinical signs of mitral stenosis are equivocal, and particularly when there is also suspicion of mitral insufficiency, aortic valve disease, or myocardial failure, right heart catheterization is not likely to be of diagnostic help, and the method of choice is percutaneous catheterization of the left heart. This was first described by Björk and associates[10] in Sweden in 1953. The technic was modified and improved by Fisher in 1954.[11] With the patient in the prone position a needle is inserted under fluoroscopic guidance through the skin of the back into the left atrium. A catheter is then passed through the needle across the mitral valve into the left ventricle. Pressures on both sides of the mitral valve are measured successively or preferably simultaneously[12] (fig. 4 bottom). The mean pressure difference (gradient) across the mitral valve during diastole is thus obtained. There is no pressure difference across the normal mitral valve during diastole (fig. 4 top). Narrowing of the mitral valve constitutes an obstruction in the face of which diastolic blood flow can only be maintained by a rise in left atrial pressure producing

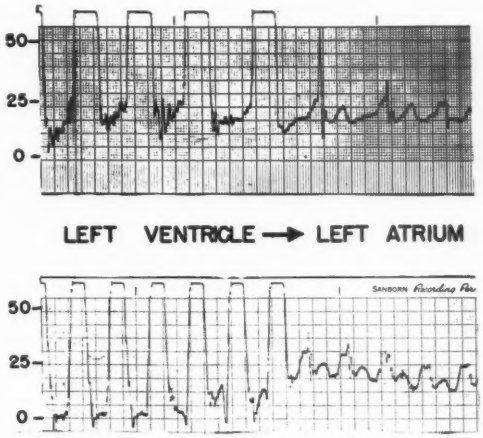


FIG. 4. Catheterization of the left heart in mitral stenosis. *Top*. The pressure tracings obtained during withdrawal of a catheter from the left ventricle to the left atrium across *a normal mitral valve* demonstrate that there is no pressure difference across the valve in diastole. *Bottom*. Withdrawal from the left ventricle to the left atrium across *a stenosed mitral valve* shows a mean diastolic pressure gradient of 17 mm. Hg. Cardiac output determined by simultaneous catheterization of the right heart was 3.8 L./min. By means of the formula of Gorlin and Gorlin[13] the diastolic mitral valve area was estimated to be 0.7 cm.^{2} Severe mitral stenosis was found at subsequent mitral valvuloplasty (D. E. H.).

a pressure difference across the mitral valve. Blood flow is a function of both the size of the valve orifice and the pressure gradient across it in diastole. If the pressure gradient and blood flow are measured simultaneously, functional valve size may be estimated from hydraulic formulas. These were developed by Gorlin and Gorlin[13] at a time when the pressure gradient could not be measured directly but only assessed as the difference between the pulmonary wedge pressure determined by right heart catheterization and an assumed left ventricular diastolic pressure.

Measurement of the pressure gradient across the mitral valve by percutaneous left heart catheterization or at the time of thoracotomy will give information as to presence or absence of obstruction, and may allow some general judgment as to its severity if the arterial blood pressure is normal. Quantification of stenosis, however, demands a simultaneous determination of the cardiac output. Left heart catheterization alone or in combination with right heart catheterization has been performed in our laboratories on approximately 150 occasions without serious complications. Our experience and that of others[12, 14] suggest that this technic carries a low risk when performed with care in selected patients. The procedure remains to be fully developed and evaluated but it shows great promise. It is the most direct physiologic approach to the mitral valve yet devised.

The Differentiation of Stenosis from Insufficiency

Surgery of mitral valve disease has made more imperative quantitative differentiation of degrees of stenosis and insufficiency and has also aided in elucidating the diagnostic criteria. It is clear that a simple diagnostic differentiation based on the presence of apical systolic or diastolic murmurs is not only inadequate but often misleading. It is true that loud apical systolic murmurs transmitted laterally suggest the presence of mitral insufficiency but they furnish little quantitative information; insufficiency may be severe with slight murmurs or insignificant with loud murmurs. Many patients have associated tricuspid insufficiency, which may give rise to systolic murmurs difficult to distinguish from those arising at the mitral valve, although they are usually not transmitted laterally of the apex. The same applies to diastolic murmurs; marked rumbling diastolic murmurs with presystolic accentuation usually mean stenosis, but stenosis may be severe with slight diastolic murmurs or rarely none at all, and patients with free insufficiency may have loud diastolic murmurs usually, however, rather early in timing. A sharp mitral first sound and an opening snap both point to stenosis.

Patients with predominant insufficiency frequently have less pulmonary hypertension and a relatively lower effective forward blood flow than those with stenosis who are at a comparable stage of the disease. Hence the former are somewhat more likely to complain of fatigue as a dominant symptom rather than dyspnea. However, too much reliance should not be placed on this differentiation because exceptions are frequent. The presence of pulmonary hypertension is reflected in an increased and often split pulmonic second sound, prominent pulmonary artery shadows shown roentgenographically, and right ventricular enlargement. All of these are more common in mitral stenosis, whereas left ventricular enlargement not otherwise explained is a sign pointing to mitral insufficiency. It is often very difficult to be sure from roentgenogram or fluoroscopy to what degree right and left ventricular hypertrophy contribute to the enlarged cardiac silhouette, especially if the left atrium is markedly dilated. The electrocardiogram is often of greater help in estimating the type of enlargement. Unusual enlargement of the left atrium is found most commonly in association with insufficiency, and in the oblique view the enlarged atrium is characteristically low and may rest on the diaphragm. Systolic expansion of this chamber has not proved to be a helpful sign in differentiation. Calcification of the valve usually means that at least some stenosis is present.

Methods for the detection of mitral insufficiency by injection of radiopaque dye into the left atrium or ventricle have been reported but are still to be considered in the experimental stage.

In summary, there is no absolute method of differentiating stenosis from insufficiency clinically. All of the evidence must be weighed and a decision reached after such total evaluation.[15] As will be seen, laboratory study helps little in this problem.

When significant amounts of blood regurgitate backward across the mitral valve in systole, forward mitral valve flow during diastole must increase if aortic valve flow or cardiac output is to be maintained. This increase in systolic flow across a narrowed mitral valve will be possible only if the pressure gradient is increased by a rise in left atrial pressure. In other words, insufficiency superimposed on anatomic stenosis of a valve increases physiologic stenosis by increasing the demand for forward flow. Since there is, as yet, no dependable method of measuring valve flow when regurgitation is present, although current work in our and other laboratories shows some promise that analysis of indicator-dilution curves may help in this regard,[12] this method of estimating valve size by means of left heart catheterization does not apply when there is valvular insufficiency. As a rule, the presence of insufficiency is signaled by a regurgitant wave inscribed on the left atrial pressure tracing. The atrial pressure tracing, however, has little quantitative value, nor does its derivative, the pulmonary wedge pressure tracing. Neither has been found helpful by us in estimating the degree of mitral insufficiency or of stenosis. Nevertheless, analysis of all clinical and physiologic data in a given patient usually permits a correct decision.

Predominant mitral insufficiency constitutes a contraindication to the conventional operation for stenosis. On the other hand, when stenosis predominates and is at least moderate in degree, surgical treatment of the stenosis alone will be followed by worth-while improvement in more than half of the patients even in the presence of insufficiency. In the past 3 years mild to moderate degrees of associated regurgitation seem to have been improved by a simple extracardiac maneuver that involves the insertion of an external baffle that tends to reduce the valvular and atrial herniation and distorts the annulus so that the leaflets approximate better. Definitive correction of regurgitation has been unsatisfactory to date.

Peripheral Embolization

This is one of the great hazards to patients with mitral stenosis, particularly if they are fibrillating. No satisfactory medical preventive treatment has yet evolved. Our experience in this regard is as follows: in 19 per cent of the first 1,000 operated patients one or more clear-cut episodes of peripheral embolization had occurred prior to operation. The present risk of developing an operative embolus in patients is 2 per cent in group III and 9 per cent in group IV, but it is twice as great in patients with a history of preoperative embolus. Once the hurdle of operation is safely passed, however, the likelihood of a late embolus appears to be slight. Of the entire group of 913 patients surviving operation 19 have developed late peripheral emboli. Since the average time of follow-up in the series is nearly 3 years, this represents an experience of more than 2,500 patient years or a rate of 0.6 per cent per year. This figure indicates that operation protects against late embolization. This presumably is due to reducing stasis in the atrium by valvuloplasty and removing a nidus of extreme stagnation by concomitant appendectomy. Operation may be recommended as a proper procedure in patients who have had previous emboli. It is probably more reliable and carries less risk than other radical treatments in the prevention of emboli in such patients.

How soon operation should be undertaken after a major peripheral embolism is uncertain. We have had considerable experience with patients operated upon hours, days, and weeks after peripheral embolization. The incidence of operative embolization is no greater than when the operation is delayed. Moreover, even after such a recent embolic phenomenon, thrombi in the atrium and atrial appendage are found at operation in only about half of the cases. Probably the ideal approach is to keep a patient on anticoagulant therapy for 3 or 4 weeks after a peripheral embolus and then operate as soon as possible after the omission of anticoagulant therapy permits the clotting mechanism to re-

turn to normal. Occasionally, the hand of the surgeon is forced in patients who are having showers of peripheral emboli. In such instances mitral valvuloplasty may actually become an emergency procedure.

Rheumatic Activity

Rheumatic activity with myocardial failure as opposed to valvular obstruction causing symptoms is a recurring problem. There is no good test for rheumatic activity. Most patients do not show the classical criteria of rheumatic fever. There is no correlation between Aschoff nodules in the auricular biopsies and the clinical course of these patients. Various laboratory tests useful in young people with active rheumatic fever are of little help in these patients, who are usually adults with subclinical rheumatic activity. Antistreptolysin titers and determinations of C-reactive protein usually are normal and sedimentation rates are not likely to be useful. Many patients with high-grade mitral stenosis, particularly those having some degree of congestive failure, show slightly elevated sedimentation rates even in the absence of any evidence of rheumatic fever. If flagrant rheumatic activity is obvious, operation should be postponed. If doubt exists as to rheumatic activity and there is clear evidence of symptoms due to obstruction, operation is usually worthwhile. This removes one cardiac burden and the patient may handle his rheumatic carditis better.

Myocardial Failure

It is often difficult if not impossible to determine clinically to what degree symptoms of pulmonary or systemic congestion are secondary to severe obstruction to blood flow or to myocardial insufficiency. Cournand and his group recently stressed the need for further study of this problem.[16] A clinical course characterized by few symptoms and little disability, interrupted periodically by acute episodes of symptoms of congestion, especially in the elderly patient, suggests that there is episodic failure of the myocardium. An unusually large heart, not explained on the basis of coexistent mitral insufficiency or aortic disease, suggests poor ventricular muscle. Right heart catheterization may give support to the suspicion of prominent myocardial disease when pulmonary hypertension is absent or mild and when the arteriovenous oxygen difference is very wide (i.e., the cardiac output very low). Since the left ventricular diastolic pressure can be measured by left-sided cardiac catheterization, a direct method of testing left ventricular competence is now available. To what extent it will be possible by such technics to apportion symptoms between valvular lesions and myocardial weakness remains to be seen, but the approach promises to be fruitful.

Associated Aortic Valvular Disease

Evidence of aortic valve deformity without significant physiologic effect does not alter the risk and prognosis of mitral valvuloplasty. Significant aortic stenosis requires an elevated left ventricular systolic pressure and increased left ventricular work. In such a situation correction of mitral stenosis alone is improper as the operative risk is increased, the benefit to be expected is uncertain, and the danger of significant postoperative mitral insufficiency quite real. The clinical problem lies in the interpretation of the signs of aortic stenosis. This will be discussed later. Significant aortic stenosis per se indicates direct surgical attack just as mitral stenosis does. If both are significant, they can be corrected simultaneously. Significant aortic insufficiency, generally manifested by a lowered diastolic blood pressure and a dilated left ventricle with increased amplitude of pulsations, contraindicates mitral valvuloplasty, but does not commonly accompany pure severe mitral stenosis. The diastolic murmur heard so frequently along the left sternal border in patients with mitral stenosis is often due to pulmonic rather than aortic insufficiency.

Associated Tricuspid Valvular Disease

Functional tricuspid insufficiency, especially in association with atrial fibrillation, is quite frequent in patients with mitral stenosis.[17] Organic tricuspid disease is fairly rare. Tricuspid stenosis does occur and its recognition is important since it is an operable lesion.[18] Functional tricuspid insufficiency is no contraindication to mitral valvuloplasty. It is likely

o improve after successful correction of stenosis. Organic tricuspid insufficiency also is likely to improve after mitral valvuloplasty reduces right ventricular systolic pressure. Finally, relative tricuspid stenosis resulting from asymptomatic asymmetric commissural fusion and tight bowstring orifice occlusion by atrial enlargement may disappear after pulmonary hypertension is relieved.

Associated Pulmonary Disease

Patients with severe pulmonary vascular disease have shown marked postoperative improvement and those with the highest pulmonary arterial pressure often benefit most. Pulmonary hypertension has fallen more rapidly than the vascular changes could be expected to subside. This leads to the hypothesis that pulmonary hypertension may be in part functional.

Significant independent pulmonary disease may affect risk and prognosis. Pulmonary emphysema increases operative risk and favors residual postoperative cardiopulmonary symptoms. Pleural disease may decrease pulmonary reserve and cause early postoperative difficulties. Tests of ventilatory function and occasionally bronchospirometry may be helpful in such problems. Prominent cough and sputum, clubbing of fingers, and polycythemia are findings that should lead to a search for pulmonary disease. An approach through the right chest has been described[19] and might be considered when there is diminished function of the right lung, and left thoracotomy could be most dangerous. Such an awkward approach, however, must be weighed against the significantly poorer quality of valvular surgery per se. Direct surgery requires the surgeon's best effort and any handicap should be gravely considered before acceptance.

Subacute Bacterial Endocarditis

This condition like thyrotoxicosis and acute rheumatic activity should arrest the attention of the careful clinician but, once reasonably excluded, should not constitute a basis for procrastination. Prompt blood cultures should be taken. If positive, surgery is deferred until the condition is controlled.

Pregnancy

Most women with the murmur of mitral stenosis can go through pregnancy without difficulty. Patients with mild symptoms often tolerate pregnancy if carefully managed. It is seldom necessary to add the hazard of an operation at the time of pregnancy. Moreover, women with or without heart disease often retain fluid, complain of dyspnea, and present other symptoms that make it very difficult to determine the extent of actual cardiac embarrassment. Murmurs and other objective cardiac signs are frequently difficult to evaluate during pregnancy. There are, however, patients with pure mitral stenosis who would have been classified in group III or IV prior to pregnancy, patients for whom valvuloplasty would have been clearly indicated. If such patients come under observation for the first time during the first trimester of pregnancy, a mitral operation can be done with little more risk than would obtain in the nonpregnant state and probably less than for the alternative courses of action: either interruption of pregnancy and then valvuloplasty, or continuation of pregnancy under medical management and then a later valvuloplasty. From the fourth to the eighth month the added risk of valvuloplasty during pregnancy is very real and a decision as to the course of action must depend on weighing all factors. After the eighth month even patients in congestive failure should not be operated upon if it can possibly be avoided, since the burden of pregnancy becomes less during the final month.

Refusion

It has been increasingly apparent that the quality of a valvuloplasty as performed by the surgeon is of paramount importance in determining long-term results. Many of the poor results and regressions are due to inadequate operations rather than refusion of the valve. Our follow-up statistics as well as those reported by others suggest that this does not occur commonly, at least in the first 5 years. However, there is little doubt that it does occur occasionally and as the years of follow-up observation lengthen, will be seen more frequently. After

all we do not know what are the factors and mechanisms that led to the development of tight mitral stenosis in the first place, usually years after the initial rheumatic infection. Such mechanisms may still be operative in many patients after mitral valvuloplasty.

Aortic Stenosis

This lesion presents a problem of a different order. Aortic stenosis calls for compensation by left ventricular hypertrophy and patients with the disease may remain asymptomatic for many years, often into old age. By the time symptoms appear, the valve is likely to be quite fixed, calcified, and associated with myocardial fibrosis. Coronary artery disease may have developed. Symptoms usually indicate a breakdown of compensatory mechanisms and herald a rapid, worsening course. The surgical approach, whether transventricular or transaortic, is more difficult and more dangerous than the approach to the mitral valve. This disease occurs most often in males, becomes symptomatic late in its course, usually in mature or later life, and generally carries a poor medical prognosis once symptomatic.[20, 21] If this is taken into account, the operative mortality of about 20 to 25 per cent for the transventricular approach and 10 to 15 per cent for the newer and preferred transortic approach does not appear prohibitive.

Diagnosis of Aortic Stenosis

A clinical diagnosis of dynamically significant aortic stenosis may be made with confidence when there is a harsh, often musical systolic aortic murmur, accompanied by a thrill, a decreased or absent second aortic sound, a small pulse, a narrow pulse pressure, and when the electrocardiogram shows left ventricular hypertrophy, and calcification of the aortic valve can be demonstrated roentgenologically. Were one to require all these features, many cases of significant aortic stenosis would be missed. In general, in aortic stenosis any 1 or 2 of these criteria may be absent, but if 3 or more are absent, severe aortic stenosis is unlikely. It must be remembered that the murmur of aortic stenosis may be loudest at the apex or even confined to this area. Its harshness and musical quality often indicate its origin.

It was formerly believed that the direct arterial pressure tracing with prolongation of the systolic upstroke and an anacrotic notch would be a useful adjunct in the diagnosis of hemodynamically significant aortic stenosis. Such tracings, indeed, constitute confirmatory evidence of the presence of aortic stenosis, but not only do not distinguish between mild and severe obstruction at the aortic valve, but may be seen in the absence of any obstruction at the valve.[22] Conversely, severe aortic stenosis may be occasionally associated with a normal arterial pressure tracing. The presence of aortic stenosis is best documented by demonstrating a systolic pressure gradient across the aortic valve. When obstruction is significant, ventricular pressure exceeds aortic pressure during systole. Since the magnitude of the systolic pressure gradient across the valve is a function of both valve size and valve flow, the degree of aortic stenosis can be determined only if the pressure gradient and cardiac output are measured simultaneously. As with mitral stenosis, catheterization of the left heart is necessary to this end (fig. 5).

Right heart catheterization is of little more than academic interest in the diagnosis of aortic stenosis, but it may have some value in

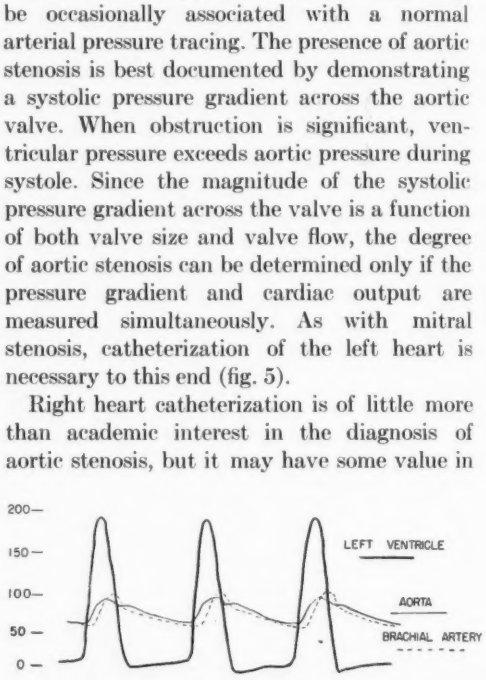


Fig. 5. Catheterization of the left heart in aortic stenosis. The pressure tracings obtained from the left ventricle, aorta, and brachial artery of a patient with calcific aortic stenosis have been redrawn and superimposed. The mean systolic pressure in the left ventricle, obtained by graphic integration, was 128 mm. Hg, and the mean systolic pressures in the central aorta and the brachial artery were identical at 68 mm. Hg. Thus the mean systolic aortic pressure gradient was 60 mm. Hg. The cardiac output determined by simultaneous catheterization of the right heart was 5.9 L./min. The calculated[13] systolic aortic valve area was 0.9 cm.^{2} Digital examination at subsequent valvulotomy (Dr. G. W. B. Starkey) revealed severe aortic stenosis.

the detection of coexistent cardiac and pulmonary disease.

Clinical Course and Prognosis

Conclusions based on retrospective reviews of anatomically proved cases of aortic stenosis[20] have limited applicability but, in general, agree with follow-up studies of patients encountered in the clinic.[21] While some patients with calcific aortic stenosis remain fully active and asymptomatic into advanced age, death often follows the onset of symptoms within months or very few years. Moreover, a significant number of patients with aortic stenosis die suddenly without the warning of symptoms, or without progression of symptoms. While angina pectoris or syncope may be present for several years, congestive heart failure is a late event and carries a poor prognosis. Atrial fibrillation is uncommon before the late stage of decompensation. Patients under 60 years of age with severe aortic stenosis and disabling symptoms have followed an especially malignant course in our experience.

Operative and Postoperative Prognosis

The early transventricular approach to the aortic valve had an immediate operative mortality of at least 20 per cent.[23] Ventricular fibrillation and hemorrhage were the chief difficulties. The procedure was blind, rapid, and uncontrolled. It carried the danger of producing free aortic insufficiency. The current transaortic route[24, 25] permits digital exploration of the valve. Often the valve fracture itself can be carried out by the finger. This technic has reduced the operative mortality to the order of 10 per cent, but the danger of inducing aortic insufficiency has not been eliminated. However, combinations of stenosis and insufficiency have been operated upon, where leaflet mobilization reduced both obstruction and reflux.

Too few cases have been followed long enough to permit any definite statement as to long-range operative benefits. However, striking symptomatic improvement, reduction in disability, and rehabilitation have followed aortic valve surgery. Left heart catheterization before and after operation has demonstrated that the functional aortic valve area can be increased. How often this can be achieved, and to what extent the long-range prognosis of aortic stenosis can be improved by operation must be established by further study. It already seems clear, however, that the intrinsic pathologic process will limit perfect surgery and be responsible for some poor results. This proper palliative surgery will eventually be supplanted by valve replacement. This hope for the future will not, however, be in the life time of patients who now have symptoms from aortic stenosis.

Coronary Disease and Myocardial Damage

The presence of coronary atherosclerosis or myocardial infarction increases the operative risk and reduces the degree of postoperative improvement. As such, coronary artery disease is a relative contraindication to operation. The incidence of coronary disease in the older patients with aortic stenosis is appreciable, but the diagnosis is difficult. Coronary atherosclerosis in combination with calcification of the aortic valve but with mild or no stenosis may mimic severe aortic stenosis. Occasionally coronary calcification may be visible radiologically. An old myocardial infarct may be demonstrable by electrocardiogram, vectorcardiogram or even radiologically. As a rule it is difficult to rule out coronary disease, and the severity of aortic stenosis has to be assessed by catheterization of the left heart. Some degree of myocardial fibrosis is present in most patients with severe aortic stenosis and does not contraindicate operation. A poor myocardium with limited blood supply should be able to function better without an aortic block.

Aortic Insufficiency

Significant aortic insufficiency represents a contraindication to operation for aortic stenosis, since regurgitation may be increased. The early diastolic murmur of aortic insufficiency often accompanies aortic stenosis and does not necessarily indicate the presence of significant aortic reflux. Mild insufficiency is no contraindication to operation if aortic stenosis is severe. When a wide pulse pressure and a diastolic pressure below 50 mm. Hg are associated with the murmur of aortic insufficiency,

aortic regurgitation is probably significant. It must be kept in mind that peripheral vasodilatation may simulate aortic insufficiency, and vasoconstriction, while actually increasing regurgitation, may decrease the peripheral signs. Direct arterial pressure tracings give more accurate information about the absolute level of diastolic and pulse pressures, but do not permit quantitation of aortic regurgitation. When left heart catheterization demonstrates only a slight systolic pressure gradient across the aortic valve in the presence of signs of stenosis and insufficiency, the latter lesion probably predominates and the operation for stenosis is contraindicated. In the presence of aortic insufficiency, standard aortic valve formulas overestimate the severity of aortic stenosis, since the increased forward aortic valve flow (cardiac output plus regurgitant flow) necessitates a larger systolic pressure gradient across the valve. Thus a method to measure total aortic valve flow is needed before the relative degrees of aortic stenosis and aortic insufficiency can be quantitatively assessed by left heart catheterization.

Other Valvular Disease

When mitral stenosis and aortic stenosis coexist and both are hemodynamically severe, the 2 conditions must be corrected at the same operation. Mitral insufficiency increases operative risk but does not contraindicate an operation for aortic stenosis. Such mitral incompetence may be improved after ventricular systolic pressure falls.

Other Factors

Bacterial endocarditis, acute rheumatic fever, and severe congestive heart failure resistant to treatment represent contraindications to surgery. Rheumatic activity is less of a problem in the older age group. Since aortic stenosis is seen mainly in men of middle age and older, chronic bronchitis and pulmonary emphysema coexist not infrequently and should be evaluated. Functionally significant pulmonary emphysema increases operative risk and affects postoperative prognosis adversely. It may even constitute a contraindication to operation.

Summary of the Indications for Operation for Aortic Stenosis

When a patient with clinically pure aortic stenosis and with no contraindications shows progressive disabling cardiovascular symptoms, catheterization of the left heart should be performed to determine the degree of aortic stenosis. If stenosis is severe, operation should be recommended. Contraindications include coronary atherosclerosis, myocardial infarction, severe aortic regurgitation, rheumatic activity, bacterial endocarditis, and intractable congestive heart failure.

Patients with significant aortic stenosis and stationary cardiac symptoms may be considered for operation, provided severe aortic stenosis can be demonstrated hemodynamically.

Patients with asymptomatic severe aortic stenosis may eventually prove to be the best surgical group, but should not be considered for operative treatment until more is known about the long-range effects of aortic valvulotomy. In all probability the limitations of the calcific pathologic process itself will continue to make such "early surgery" improper until valve replacement is possible.

REFERENCES

1 Ellis, L. B., and Harken, D. E.: The clinical results in the first five hundred patients with mitral stenosis undergoing valvuloplasty. Circulation **11:** 637, 1955.

2 Soulié, P., Di Matéo, J., and Azerad, J.: Résultats de la commissurotomie pour retrécissement mitral (à propos de 213 interventions). Bull. et mém. d. hôp. de Paris nos. 21–22, 742, 1955.

3 Bailey, C. P., and Bolton, H. E.: Criteria for and results of surgery for mitral stenosis. Part II: Results of mitral commissurotomy. New York J. Med. **56:** 825, 1956.

4 Janton, D. H., Davila, J. C., and Glover, R. P.: Status of fifty patients four and a half to seven years after mitral commissurotomy. Circulation **14:** 175, 1956.

5 Grant, R. T.: After histories for ten years of one thousand men suffering from heart disease. Heart **16:** 275, 1933.

6 Wilson, J. K., and Greenwood, W. F.: The natural history of mitral stenosis. Canad. M.A.J. **71:** 323, 1954.

[7] HAMILTON, B. E., AND THOMSON, K. J.: The Heart in Pregnancy and the Child Bearing Age. Boston, Little, Brown & Company, 1941, pp 402.

[8] OLESEN, K. H.: Mitral Stenosis: A follow-up of 351 patients. Copenhagen, Ejnar Munksgaards Forlag, 1955, pp 228.

[9] BRUCE, R. A., MERENDINO, K. A., PAMPUSH, J. J., BERGY, G. G., AND BROCK, L. L.: Functional evaluation of mitral valvulotomy. Superiority of hemodynamic evaluations in selecting patients. Am. J. Med. **20:** 745, 1956.

[10] BJÖRK, V. O., MALMSTROM, G., AND OGGLA, L. G.: Left auricular pressure measurements in man. Ann. Surg. **138:** 718, 1953.

[11] FISHER, D. L.: The use of pressure recordings obtained at transthoracic left heart catheterization in the diagnosis of valvular heart disease. J. Thoracic Surg. **30:** 379, 1955.

[12] BURCHELL, H. B., ET AL.: Symposium on the diagnostic value of simultaneous catheterization of the aorta and the right and left sides of the heart. Proc. Staff Meet., Mayo Clin. **31:** 105, 1956.

[13] GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. Am. Heart J. **41:** 1, 1951.

[14] LAWRENCE, G. H.: Risk of catheterization of the left side of the heart. New England J. Med. **225:** 180, 1956.

[15] ABELMANN, W. H., ELLIS, L. B., AND HARKEN, D. E.: The diagnosis of mitral regurgitation. An evaluation of clinical criteria, fluoroscopy, phonocardiogram, auricular esophagogram and electrokymogram. Am. J. Med. **15:** 5, 1953.

[16] FERRER, M. I., HARVEY, R. M., WYLE, R. H., HIMMELSTEIN, A., LAMBERT, A., KUSCHNER, M., COURNAND, A., AND RICHARDS, D. W.: Circulatory effects of mitral commissurotomy with particular reference to selection of patients for surgery. Circulation **12:** 7, 1955.

[17] SEPULVEDA, G., AND LUKAS, P. S.: The diagnosis of tricuspid insufficiency. Clinical features in 60 cases with associated mitral valve disease. Circulation **11:** 552, 1955.

[18] YU, P. N., HARKEN, D. E., LOVEJOY, F. W., JR., NYE, R. E., JR., AND MAHONEY, E. B.: Clinical and hemodynamic studies of tricuspid stenosis. Circulation **13:** 680, 1956.

[19] NEPTUNE, W. B., AND BAILEY, C. P.: Mitral commissurotomy through the right thoracic approach. J. Thoracic Surg. **28:** 15, 1954.

[20] BERGERON, J., ABELMANN, W. H., VAZQUEZ-MILAN, H., AND ELLIS, L. B.: Aortic stenosis—clinical manifestations and course of the disease. Review of one hundred proved cases. Arch. Int. Med. **94:** 911, 1954.

[21] MITCHELL, A. M., SACKETT, C. H., HUNZICKER, W. J., AND LEVINE, S. A.: The clinical features of aortic stenosis. Am. Heart J. **48:** 684, 1954.

[22] HANCOCK, E. W., ABELMANN, W. H., AND WALKER, R. P.: The clinical interpretation of brachial artery pressure tracings. Proc. New England Cardiovasc. Soc. **14:** 33, 1956.

[23] LIKOFF, W., BERKOWITZ, D., DENTON, C., GOLDBERG, H., AND REALE, A.: Transventricular commissurotomy in aortic stenosis. A clinical evaluation. J.A.M.A. **157:** 1367, 1955.

[24] URICCHIO, J. F., LITWAK, R., DENTON, C., GOLDBERG, H., AND LIKOFF, W.: A medical appraisal of transaortic commissurotomy. Ann. Int. Med. **44:** 844, 1956.

[25] HARKEN, D. E., AND WILSON, H.: Aortic stenosis. *In* Lewis-Walters, Practice of Surgery. Hagerstown, W. F. Prior Co., 1956, In press.

I hold every man a debtor to his profession; from the which as men of course do seek to receive countenance and profit, so ought they of duty to endeavor themselves by way of amends to be a help and ornament thereunto.—FRANCIS BACON, 1561–1626.

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

Abstracters

DOMINGO, M. AVIADO, JR., M.D., Philadelphia
ARTHUR BERNSTEIN, M.D., Newark
MASSIMO CALABRESI, New Haven
CHARLES D. ENSELBERG, M.D., New York
RAYMOND HARRIS, M.D., Albany
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
EUGENE LEPESCHKIN, M.D., Burlington
MORTON H. MAXWELL, M.D., Los Angeles
VICTOR A. MCKUSICK, M.D., Baltimore
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
FRANCIS F. ROSENBAUM, M.D., Milwaukee
ELLIOT L. SAGALL, M.D., Boston
DAVID SCHERF, M.D., New York
JOHN B. SCHWEDEL, M.D., New York
CHARLES R. SHUMAN, M.D., Philadelphia
FRANKLIN SIMON, M.D., Newark
LOUIS A. SOLOFF, M.D., Philadelphia
S. O. WAIFE, M.D., Indianapolis
RICHARD WECHSLER, M.D., Pittsburgh
MARTIN WENDKOS, M.D., Philadelphia

ATHEROSCLEROSIS

Hanig, M., Shainoff, J. R., and Lowy, A. D., Jr.: Flotational Lipoproteins Extracted from Human Atherosclerotic Aortas. Science **124:** 176 (July 27), 1956.

In this study, lipoproteins were extracted from human atherosclerotic aortas. The material was extracted from the intima and, when suitably prepared, was thereafter treated exactly as the lipoprotein flotational preparations and analyzed in the usual manner. The observations indicate an almost perfect correlation among the plaques, the presence of a cardiovascular death, and the presence of the S_f 12–100 fractions in aortas. The most prominent lipoprotein fraction occurring in serum, the S_f 0–12 fraction was absent in these aortic extracts, regardless of the presence or absence of plaques. This would imply that the S_f 0–12 fraction is unassociated with atherosclerotic activity and is a normal component of serum. On the other hand, the S_f 12–100 fraction is always present in substantial amounts in aortas that show atherosclerosis. The presence of plaques and the S_f 12–100 fraction in the aorta appeared in 10 of 11 cardiovascular deaths. Even among noncardiovascular deaths, when plaques were present, substantial concentrations of this S_f 12–100 fraction were present, but the fraction was absent when the plaques were not found.

WAIFE

Weens, H. S., and Marin, C. A.: Infantile Arteriosclerosis. Radiology **67:** 168 (Aug.), 1956.

The authors describe 2 infants 25 days and 16 months of age respectively with extensive arteriosclerotic lesions involving the medium and small arteries of many viscera, including the heart. Characteristic is the fragmentation of the internal elastic membrane, intimal and medial calcification and fibroblastic intimal proliferation to the point of vascular occlusion. No intimal lipid deposition was found. Etiologic factors considered were renal disease, hyperparathyroidism, and vitamin D intoxication, and progeria, but these entities were absent in the 2 cases presented here.

Roentgenologic technics may demonstrate intimal and medial calcification, particularly applicable to visualization of opacified arteries in the extremities.

SCHWEDEL

Parsons, W. B., Jr., Achor, R. W. P., Berge, K. G., McKenzie, B. F., and Barker, N. W.: Changes in Concentration of Blood Lipids Following Administration of Large Doses of Nicotinic Acid to Persons with Hypercholesterolemia: Preliminary Observations. Proc. Staff Meet., Mayo Clin. **31:** 391 (June), 1956.

Administration of large doses of nicotinic acid to patients with hypercholesterolemia and an abnormally high ratio of beta-lipoprotein cholesterol to alpha-lipoprotein cholesterol (beta/alpha ratio) caused the pattern of the blood lipids to change toward normal in the majority of patients. The plasma cholesterol decreased significantly in 9 of 13 patients observed for 12 weeks and in 3 of 5 other patients observed for 4 weeks. The beta/alpha ratio was reduced in 11 of 13 patients observed for 12 weeks and in 4 of 5 patients observed for 4 weeks. The concentration of total lipids in the plasma was reduced in most of the patients but to a lesser degree than was the concentration of cholesterol.

Side reactions, consisting of flushing and pruritus, tended to diminish rapidly after the first few days of treatment. Urticaria, nausea, and vomiting, which were observed in a few patients, subsided when the drug was withheld temporarily and did not recur when administration was resumed.

SIMON

Miasnikov, A. L.: Effect of Some Neurotropic Drugs on Blood Cholesterol in Persons with Atherosclerosis. Klin. med. **37**/6: 65 (June), 1956.

In all of 79 persons with atherosclerosis and 17 with duodenal ulcers, chloral hydrate or amytal sodium in hypnotic doses caused decrease of serum cholesterol averaging 33 and 25 mg. per cent respectively, while phenamine or caffeine caused elevation averaging 25 and 26 mg. per cent respectively. Free and ester cholesterol were equally affected. The lecithin concentration, determined in a smaller group, showed a smaller and less constant rise after both phenamine and amytal sodium.

LEPESCHKIN

Kritchevsky, D., Moyer, A. W., Tesar, W. C., McCandless, R. F. J., Logan, J. B., Brown, R. A., and Englert, M.: The Effect of Sodium 2-Phenylbutyrate in Experimental Atherosclerosis. Angiology **7:** 156 (Apr.), 1956.

The hypocholesterolemic action of sodium 2-phenylbutyrate was investigated in a series of normal rabbits in which the drug was added to the diet. On the basis of control studies, it was found that the drug had lowered the serum cholesterol levels. Atheromatous lesions, however, were not significantly reduced in the aorta. The use of this agent was complicated by the occurrence of hemorrhagic kidneys in several treated animals.

WESSLER

Altschul, R.: Influence of Nicotinic Acid on Blood Cholesterol and Experimental Atherosclerosis. Ztschr. Kreislaufforsch. **45:** 573 (aug.), 1956.

Relatively high doses of nicotinic acid seem to cause a decrease of serum cholesterol in human beings and in rabbits. When nicotinic acid was given rabbits together with cholesterol for 3 months, the development of atherosclerosis was inhibited or completely prevented in most of the animals.

LEPESCHKIN

Piper, J., and Orrlid, L.: Essential Familial Hypercholesterolemia and Xanthomatosis. Follow-up Study of Twelve Danish Families. Am. J. Med. **21:** 34 (July), 1956.

The authors present a follow-up study of 50 persons with essential familial hypercholesterolemia, representing 12 families previously studied from 1941 to 1943. Hypercholesterolemia without xanthomatosis was the rule in children and young adults; hypercholesterolemia with xanthomatosis in older adults. In each individual xanthomatosis had a tendency to progress. Regression of the lesion was exceptional. Hypercholesterolemia was present from childhood. The serum cholesterol increased steadily from childhood until the fifth decade, after which it seemed to decrease. This corresponds with the findings in normocholesterolemic persons. Essential familial hypercholesterolemia was transmitted as a dominant. The occurrence of xanthomas was not conditioned by homozygous heredity but depended largely upon the level of serum cholesterol. Angina pectoris was common and coronary occlusion was the most common cause of sudden death, often at a relatively early age.

HARRIS

Sachs, B. A., and Weston, R. E.: Sitosterol Administration in Normal and Hypercholesteremic Subjects. Arch. Int. Med. **97:** 738 (June), 1956.

The effect of an orally administered mixture of β- and dihydro-β-sitosterols on the serum lipids of human subjects was investigated. Nine studies, including double-blindfold experiments on 5 normal subjects revealed an average mean fall of 13.0 per cent and an average maximal fall of 20.9 per cent in serum cholesterol level during sitosterol therapy. One subject with xanthomatosis exhibited a mean fall of 20.3 per cent and a maximal fall of 31.5 per cent in serum cholesterol. Although her cholesterol level did not decrease to normal values, her S_f 10–30 lipoprotein fraction did. The xanthomata stopped growing during sitosterol therapy but again grew rapidly when sitosterol was discontinued. When sitosterol was administered, there was a rise in bile cholesterol concentration of a subject with biliary cirrhosis and a bile fistula. The significance of this observation cannot be evaluated, because the spontaneous fluctuations in bile cholesterol over prolonged periods of time are not known.

Subjects failing to take sitosterol immediately prior to eating did not exhibit sustained reductions in serum cholesterol levels. In some patients with disorders of lipid metabolism, a rise in serum cholesterol levels was noted during sitosterol administration. It is suggested that in these subjects either decreased absorption of cholesterol may stimulate increased endogenous production or small amounts of sitosterol may be absorbed, poorly removed from the circulation, and spuriously analyzed as cholesterol in the serum.

BERNSTEIN

Martt, J. M., and Connor, W. E.: Idiopathic Hyperlipemia Associated with Coronary Atherosclerosis. Arch. Int. Med. **97:** 492 (April), 1956.

A case is presented of idiopathic hyperlipemia with severe coronary atherosclerosis, coronary occlusion, and myocardial infarction demonstrated at autopsy. Although idiopathic hyperlipemia is recognized to be associated with clinical coronary artery disease, this is the first recorded case of idiopathic hyperlipemia with postmortem evidence of coronary aterhosclerosis. The vitamin-A-tolerance test revealed a marked decrease in tolerance, with extremely high levels of serum vitamin A at 5 hours, supporting the prevailing concept of the pathologic physiology of this entity, i.e., an impaired or delayed clearance of dietary fats from the serum. The treat-

ment of this disease consists of a low-fat diet, which often results in prompt alleviation of symptoms of angina pectoris and abdominal pain often seen in these patients. Heparin given intramuscularly or intravenously may be helpful if dietary control is not effective.

BERNSTEIN

BLOOD COAGULATION AND THROMBOEMBOLISM

Quick, A. J., and Hussey, C. V.: Hemophilia: Quantitative Studies of the Coagulation Defect. Arch. Int. Med. **97:** 524 (May), 1956.

A new test is described for the quantitative estimation of the thromboplastinogen concentration of the blood. It is based on the principle of the prothrombin-consumption procedure modified by the addition of an extract of hemolyzed erythrocytes and plasma from a severe hemophiliac. The method is sensitive to concentrations of thromboplastinogen less than 0.1 per cent of normal.

In severe hemophilia only a trace of thromboplastinogen is present in the blood and, even at a level of 0.5 per cent, the bleeding tendency is severe. A fairly close relation between the concentration of thromboplastinogen, the clotting time, and the severity of the bleeding state exists. A transfusion of fresh blood or plasma can elevate the level of thromboplastinogen in a hemophiliac sufficiently to effect fairly normal, though temporary, hemostasis. Although the thromboplastinogen disappears fairly rapidly from the blood, as much as 0.5 per cent or more often remains 24 hours after a single transfusion of 500 ml. of blood in an adult.

BERNSTEIN

Clatanoff, D. V., and Meyer, O. O.: Further Observations on Use of Warfarin Sodium in Anticoagulant Therapy. Arch. Int. Med. **97:** 753 (June), 1956.

An interrupted schedule of administering maintenance doses of warfarin sodium every third or fourth day has been tried and appears not to be satisfactory in view of the wide fluctuation of prothrombin levels. Administration of warfarin sodium guided by the daily prothrombin determination would seem to be the best method and, if a pattern is established, the prothrombin determinations can safely be reduced in frequency. Individual dosage requirements vary widely, but for the majority, after an initial dose of 75 mg., daily or every-other-day, doses of 12.5 mg. will satisfactorily maintain a proper hypoprothrombinemia.

BERNSTEIN

Shoshkes, M., and Perelman, A. J.: Vitamin K_1 in Treatment of Bishydroxycoumarin-Induced Hypoprothrombinemia. J.A.M.A. **161:** 1145 (July 21), 1956.

Prolonged anticoagulant therapy is presently part of the accepted treatment for certain illnesses associated with actual or threatened thrombo embolic phenomena. The use of a variety of hypo prothrombinemia-producing drugs still carries dan ger of unforeseen and uncontrollable hemorrhag The use of 50 to 100 mg. doses of vitamin K_1 emu sion administered intravenously will reverse th elevated prothrombin time. The use of vitamin K intramuscularly is unpredictable. When the nee for this vitamin is urgent, as in excessive an dangerous drug-induced hypoprothrombinemia, i should always and only be injected intravenously

KITCHELL

Spaet, T. H., Bauer, S., and Melamed, S.: Hemorrhagic Thrombocythemia. A Blood Coagulation Disorder. Arch. Int. Med. **98:** 377 (Sept.), 1956.

A case of hemorrhagic thrombocythemia is reported. The patient had platelet counts reaching 10,000,000 per cubic millimeter and presented a variety of hemorrhagic manifestations. Undiluted, the platelets showed anticoagulant activity in the thromboplastin generation test but failed to show this activity when diluted to normal levels. Normal platelets showed similar anticoagulant properties when concentrated to thrombocythemic concentrations. It is suggested that the fundamental defect in hemorrhagic thrombocythemia is a coagulation disorder resulting from the anticoagulant effect of excess platelets.

BERNSTEIN

CONGENITAL ANOMALIES

Emanuel, R., and Pattinson, J. N.: Absence of the Left Pulmonary Artery in Fallot's Tetralogy. Brit. Heart J. **18:** 289 (May), 1956.

The authors report 2 cases of Fallot's tetralogy with absent left pulmonary artery. Seventeen similar cases were found in the literature. The right pulmonary artery was absent in 1 patient with Fallot's tetralogy and dextrocardia. A right-sided aortic arch was found in 60 per cent of these 21 cases compared to 20 per cent in the ordinary type of Fallot's tetralogy.

In contrast, in 17 of 19 cases with 1 pulmonary artery and normal development of the bulbus cordis, the right was the absent one.

These findings are best explained by Bremer's theory of the asymmetric development of the pulmonary arteries.

SOLOFF

Gresham, G. A.: Premature Obliteration of the Foramen Ovale. Brit. Heart J. **18:** 296 (May), 1956.

The author reports a case of premature closure of the foramen ovale in a cyanotic and dyspneic infant who died 3 hours after birth. Eight other cases were found in the literature.

All 9 cases had progressive cyanosis leading to death. Microscopically, fibroelastosis of the left ventricular endocardium was found. These constant findings support the view that anoxia of the ventricular endocardium plays a part in the production of fibroelastosis.

SOLOFF

Bing, R. J.: Homeostatic Aspects of Congenital Heart Disease. Bull. St. Francis Hosp. and Sanatorium **13:** 1 (Jan.–Apr.), 1956.

The author discusses some of the homeostatic mechanisms that come into play in congenital heart disease. Obstruction of blood flow and the shunt are the primary causes of disturbance in internal environment. The physiologic alterations in congenital heart disease can be divided into (a) disturbances in pressure and flow, and (b) disturbances resulting from the diminution of partial pressure of oxygen in arterial blood. In congenital heart disease the gradient between the pO_2 of inspired air and pO_2 of alveolar air is diminished because of hyperventilation. In the presence of a right to left intracardiac shunt there is a large drop between the oxygen tension of the alveolar and arterial pO_2 which obviates the effect of hyperventilation. The reduction in the final gradient in pO_2 from arterial to capillary blood can be due to 3 causes: the shape of the dissociation curve, the increase in cardiac output, and increase in the number of red cells. In congenital heart disease with cyanosis, the dissociation curve is the main factor in the diminution of the third or final gradient.

Under ordinary conditions hyperventilation produces either compensated or uncompensated carbon dioxide deficit, depending upon the severity and duration of the hyperventilation. If the carbon dioxide tension decreases proportional to the alkali reserve, the pH value of the blood remains constant. This occurs in the cyanotic type of congenital heart disease. There is a significant reduction in total carbon dioxide of blood; the pH remains within normal range. Consequently the reduction in alkali reserve must have been accompanied by decrease in the partial pressure of carbon dioxide. Patients with congenital heart disease generally have low alkaline reserve. An increase in the red cells and the hemoglobin of blood is constant in the cyanotic type of congenital heart disease. In all likelihood a humoral substance is released that produces increased erythropoiesis. Hypochromia due to defective iron assimilation is a common feature of congenital cyanotic heart disease. In addition to the physiochemical adjustment to anoxia there are also circulatory regulatory mechanisms in the cyanotic congenital heart disease. These include the development of collateral circulation to the lung and postural effects that can increase the arterial oxygen saturation.

HARRIS

Seppals, T., Heikel, P. E., Kyllonen, K. E. J., and Sipila, W.: Pulmonary Atresia in Tetralogy of Fallot. Ztschr. Kreislaufforsch. **45:** 409 (June), 1956.

Angiocardiography in a 4-year-old girl showed complete atresia of the left main branch of the pulmonary artery and stenosis of the right branch, while in a 21-year-old woman it showed complete atresia of the main trunk and of the right main branch, with persistence of the ductus arteriosus. In such cases temporary clamping of one of the branches during the Blalock-Taussig operation may be very dangerous.

LEPESCHKIN

Flehmig, R.-W., and Priess, H.: Differential Diagnosis of Dextracardia. Ztschr. Kreislaufforsch. **45:** 272 (Apr.), 1956.

While cases of mirror-image dextrocardia show complete inversion of all waves in lead I, those of dextroposition about a sagittal axis show normal P and QRS in lead I. The 2 cases described here showed normal precordial leads, but the transition zone was displaced to V_1–V_2 or V_2–V_3; 1 case showed transient inversion of T in lead I during an acute abdominal inflammation. In a case of dextroversion about a vertical axis, which is always congenital, P was upright in lead I but deep Q waves and inverted T waves were present in leads I and II; rS was present in V_{5r}, Rs in V_{4r} and qR in V_{3r} through V_6. The x-ray showed the aorta to be on the left side, the heart completely on the right side.

LEPESCHKIN

Mahaim, C., and Rivier, J. L.: Diagnostic Possibilities of Ebstein's Disease. Cardiologia **29:** 81 (Fasc. 2), 1956.

Following review of the literature and description of a personal observation, anatomic, clinical, and diagnostic features of Ebstein's disease are discussed. It is defined as a malformation of the tricuspid valve, the insertion of which is displaced toward the apex of the heart. In most cases this is associated with patency of the foramen ovale and pronounced dilatation of the right heart. The condition is not particularly rare and often well tolerated (cases surviving to 60 years and more have been reported). The main danger consists in a hyperexcitability of the myocardium, which can result in sudden cardiac death. For this reason catheterization is dangerous and should be avoided, particularly since the diagnosis can be made without difficulty on clinical grounds. Presenting clinical signs are cyanosis, dyspnea, and often right heart failure. On fluoroscopy, the heart is enlarged with feeble contractions and the lung fields are very translucent. The electrocardiogram shows in 90 per cent a right bundle-branch block; the P waves are often unusually tall. Additional abnormalities found are a P-R prolongation and sometimes the Wolff-

Parkinson-White syndrome. Angiocardiography reveals dilatation of the right heart chambers, the presence of an interatrial communication, slow emptying of the right ventricle, and poor opacification of the pulmonary arteries, and sometimes segmentation of the right ventricular shadow. An attempt at surgical correction is dangerous and, in the opinion of the authors, contraindicated.

PICK

Downing, D. F., and Goldberg, H.: Cardiac Septal Defects II. Atrial Septal Defect. Analysis of One Hundred Cases Studied During Life. Dis. Chest **29:** 492 (May), 1956.

One hundred consecutive patients in whom an atrial septal defect was demonstrated and who were studied by right heart catheterization were analyzed. The malformation produced symptoms in the majority of patients. Cardiac failure was common, and the authors were convinced that one reason for the oft-repeated view that atrial septal defect is commonly complicated by pneumonia is the improper interpretation of signs of heart failure. The most characteristic roentgen feature was the presence of marked dilatation of the left and right branches of the main pulmonary artery. This was seen much less frequently in other lesions allowing a left to right shunt. The electrocardiogram showed evidence of right ventricular hypertrophy in the majority. Right bundle-branch block was less than half as common. Although pulmonary hypertension was found very frequently, the pressure tended to be lower than in ventricular septal defects. The left-to-right shunt, on the other hand, tended to be greater. The mechanism of development in both atrial and ventricular septal defects of pulmonary hypertension is the same. However, initial and potential flow through a defect in the interventricular septum is greater than that through one of similar size in the atrial septum. The stimulus to pulmonary vascular changes is greater and the necessity more acute in the former.

There are no characteristic historical or physical findings. Although right bundle-branch block and marked dilatation of the primary branches of the pulmonary artery in a patient with a systolic murmur at the base allows one to be very suspicious of the presence of an atrial septal defect, the diagnosis depends upon cardiac catheterization.

Patients may be divided into 5 classes so far as the desirability of surgical closure is concerned. The magnitude and direction of shunt through the defect and the height of pulmonary pressure are the basic considerations. Defects in the septum just above the atrioventricular valves are extremely difficult to close if there is not at least a small rim of septal tissue in the area; and the attempt is extremely hazardous because of the possibility of injuring conduction tissue or of destroying the integrity of either of the atrioventricular valves which lie so close. Unfortunately, at the present time only surgical exploration allows diagnosis of the anatomic conditions, and whether or not surgical correction can be attempted.

MAXWELL

Prätan, J., and Gehmacher, K.: The Peripheral Rheogram in Congenital Heart Disease. Ztschr. Kreislaufforsch. **45:** 265, (Apr.), 1956.

Observations in 45 cases show that in persistent ductus the beginning of the pulse wave in the electric plethysmogram is earlier, the entire duration is shorter, and secondary waves are less pronounced. In coarctation of the aorta the curves in the lower extremities begin later and become more similar to sinusoidal oscillations. The later appearance of the apex in Fallot's tetralogy can be explained by a different course of aortic ramifications. The changes in other types of congenital disease are less constant.

LEPESCHKIN

Bär, C. G.: The Electrocardiogram in Hypertension. Observations in Coarctation of the Aorta. Ztschr. Kreislaufforsch. **45:** 259 (Apr.), 1956.

Of 60 patients with coarctation submitted to operation, 17 had normal electrocardiograms; among these were cases with systolic pressures exceeding 200 mm. Some of these cases had high voltage in the precordial leads, which was present in a total of 40 cases. Twenty-two patients showed low T and depressed S-T in left ventricular precordial leads and 12 also had incomplete right bundle-branch block; of these, only 3 showed increased right ventricular pressures. Four of the 6 cases with persistent ductus arteriosus had a right ventricular hypertrophy and strain pattern. After end-to-end anastomosis of the aorta the electrocardiographic changes disappeared completely in half the cases, and incompletely in the rest. The normalization was parallel to normalization of the blood pressure and took place at a time when the roentgenologically determined left ventricular hypertrophy and the high voltage were little changed. It is concluded that the left ventricular strain pattern is the result of functional rather than anatomic changes in the heart.

LEPESCHKIN

CORONARY ARTERY DISEASE

Bakst, A. A., Maniglia, R., and Bailey, C. P.: The Physiologic Explanation of the Changes in the Coronary Circulation Following Prolonged Aortico-Coronary Sinus Anastomosis. J. Clin. Invest. **35:** 302 (March), 1956.

In 2 groups of dogs, the coronary sinus was arterialized by a venous graft between the aorta and coronary sinus. With the graft open, the coronary-sinus pressure was within the range of the systemic circulation, and the coronary sinus blood was of high oxygen content. When the graft was occluded, both pressure and oxygen content reverted to those of the

normal coronary sinus. However, the authors were unable to demonstrate any retrograde perfusion of the myocardial capillary bed. After 6 months of aortico-coronary sinus arterilization, neither the quantity nor the oxygen content of the retrograde coronary arterial flow was affected by the presence or absence of a functioning sinus vein graft. The authors were unable to demonstrate any protective effect upon the myocardium against ventricular fibrillation following coronary arterial occlusion.

WAIFE

Merrill, J. M., Lemley-Stone, J., Grace, J. T. Jr., and Meneely, G. R.: Recent Clinical Experiences with Serum Aminopherase (Transaminase) Determinations. J. A. M. A. **160:** 1454 (April 28), 1956.

A significant rise in the serum aminopherase (transaminase) level after myocardial infarction has confirmed the earlier observations of other workers. Forms of heart disease unassociated with myocardial tissue damage have not demonstrated this rise. The authors, however, noted significant elevations above the normal controls (which ranged from 10 to 45 units per milliliter of serum) with skeletal muscle necrosis, liver disease, and with infarction of the liver and other abdominal viscera. It is concluded, therefore, that elevations in serum aminopherase level are associated with cellular injury of various tissues and are not related specifically to myocardial damage. Because significant elevations in serum aminopherase level do occur in a variety of clinical conditions, the physician must interpret the results of this test in the light of the entire clinical picture.

KITCHELL

Achor, R. W. P., Futch, W. D., Burchell, H. B., and Edwards, J. E.: The Fate of Patients Surviving Acute Myocardial Infarction. A Study of Clinical and Necropsy Data in Two Hundred Fifty Cases. Arch. Int. Med. **98:** 162 (Aug.), 1956.

Two hundred fifty hearts with gross myocardial scars indicative of healed infarction were selected from necropsies performed at the Mayo Clinic during the 5-year period 1946 through 1950 and studied with regard to the pathologic anatomy and its correlation with the clinical features. The cause of death was primarily of cardiac origin in nearly two thirds of the patients. There were 3 major types of cardiac death: death from congestive heart failure, death from recurrent acute myocardial infarction, and "sudden death" without congestive failure or acute infarction. The last-mentioned mechanism was the commonest of the 3 and was infrequently associated with recent coronary thrombosis.

For the patients whose acute myocardial infarction was diagnosed clinically the average length of survival following recovery from the acute episode was 43 months. Only 24 per cent of these patients survived 5 years or more, and only 7 per cent survived 10 years or longer. The period of highest mortality was within the first year after the acute illness. From the standpoint of cardiac morphology and clinical features the patients surviving 5 years or longer did not differ significantly from those of the entire series. Hence, it was concluded that the subsequent course of patients who had survived an episode of acute myocardial infarction could not be accurately predicted on the basis of morphologic or clinical findings.

BERNSTEIN

Lee, K. T., and Thomas, W. A.: Myocardial Infarction: Changing Sex Ratio and Other Factors. An Epidemiological Study of Acute Myocardial Infarction Based on the Experience of Barnes Hospital for Forty-Five Years. Arch. Int. Med. **97:** 421 (April), 1956.

Data pertaining to some epidemiologic aspects of acute myocardial infarction were obtained from a survey of the autopsy and clinical records of Washington University and Barnes Hospital, covering the period 1910–1954. The incidence of acute myocardial infarction was established in this large autopsy series (500 among 8183 adults) as a basis for comparison with other similar groups. The incidence of acute myocardial infarction has increased tremendously in all age groups in this autopsy series in the last 45 years. The incidence is 20 times greater in the decade 1945–1954 than in the decade 1910–1919. This increase is explained at least in part by the changing character of medical care and illustrates the necessity of taking into account the local customs regarding medical care in analyzing data from other parts of the world. However, the increase may reflect, in part, an actual increase in the incidence of the disease in the population and may be related to some changing factors in our civilization.

The most remarkable observation made is that the incidence of acute myocardial infarction in the 2 sexes differs only slightly when the proportion of men to women in the entire autopsy series is taken into consideration (1.2 males to 1 female). Even more remarkable is the observation that a change in this ratio occurred about 1940. For the period 1910–1939 the corresponding ratio was 2:1. For the period 1940–1954 it was 1.1:1. The fact that there were more patients with acute myocardial infarction in the autopsy series after 1939 than prior to 1939 accounts for the 1.2:1 ratio for the entire period 1910–1954. The data obtained from this series support previous observations indicating that the peak of incidence occurs later in women than in men. The incidence is proportionately higher in white persons than in Negroes in this series. Diabetes mellitus was much commoner among patients with acute myocardial infarction than it was in the general autopsy population.

BERNSTEIN

Siegel, A., and Bing, R. J.: Plasma Enzyme Activity in Myocardial Infarction in Dog and Man. Proc. Soc. Exper. Biol. & Med. **91:** 604 (April), 1956.

In dogs after experimental myocardial infarction and in human beings suffering from coronary occlusion, the plasma levels of transaminase, aldolase, isomerase, and malic acid dehydrogenase are increased. The release of enzymes into the plasma was correlated with the extent of muscle necrosis. The additional observation in dogs of negative pyruvate balance (higher concentration of pyruvate in coronary sinus than in arterial blood) appeared to be an immediate response of hypoxic myocardium.

AVIADO

Sahagun, E., and Burns, R. O.: Perforation of the Interventricular Septum Following Acute Myocardial Infarction: A Report of Four Cases Diagnosed Ante Mortem. Ann. Int. Med. **44:** 657 (April), 1956.

In 4 fatal cases of acute myocardial infarction, 3 of whom were autopsied, there developed during the early phase of the illness, a rough systolic precordial murmur. This was interpreted during life to indicate that a perforation of the interventricular septum had occurred. In the autopsied patients the diagnosis was confirmed. No characteristic electrocardiographic changes were noted that would have been helpful in substantiating the clinical diagnosis of septal rupture.

WENDKOS

Volk, B. W., Losner, S., Aronson, S. M., And Lew, H.: Serum Aldolase Level in acute Myocardial Infarction. Am. J. M. Sci. **232:** 38 (July), 1956.

The glycolytic enzyme, aldolase, is found in both skeletal and cardiac muscle and may be expected to be increased in serum in myocardial infarction due to its release from damaged cells. To investigate this assumption, 22 dogs were subjected to coronary artery ligation and 8 patients with myocardial infarction were studied. Serum aldolase measurements were determined daily on the experimental animals and patients. In 12 dogs, the descending branch of the left coronary artery was ligated just below the bifurcation and in 10 dogs a low ligation was performed. There was a prompt rise of serum aldolase in the coronary-ligated dogs. A semiquantitative relationship was found between the areas of myocardial necrosis and the levels of serum aldolase in these 2 groups of animals. In patients with acute myocardial infarction a rise in serum aldolase was noted that approximated the severity of the clinical course. In 5 additional patients with coronary insufficiency there was no rise in serum aldolase. The simplicity of the procedure may recommend it as an additional tool for the diagnosis and evaluation of therapy and prognosis in patients with myocardial infarction.

SHUMAN

Kirkeby, K.: Diagnostic and Prognostic Significance of Eosinopenia in Acute Myocardial Infarction. Am. J. M. Sc. **232:** 50 (July), 1956.

Daily eosinophil counts were performed in 149 patients in the early phase of acute myocardial infarction to evaluate the effect of the condition upon the nonspecific index of stress. In the great majority of patients an early eosinopenia of 2 days' duration or more was found. The decrease in eosinophils usually developed within a period from 5 to 48 hours. Of the counts made on the first, second, and third days only 3, 6 and 15 per cent respectively were above 50 per mm. In 81 patients with eosinopenia of less than 7 days' duration, only 2 patients died. In 23 patients with prolonged eosinopenia, 16 patients died. A normal eosinophil count in the period from 5 to 48 hours following symptoms suggestive of myocardial infarction strongly contradicts the diagnosis. An early eosinopenia was found frequently in pneumonia, pulmonary embolism, arrhythmias, acute congestive failure, and gallbladder disease. Uncomplicated angina pectoris was not associated with significant eosinopenia. A reduction of eosinophils is of no value in the differential diagnosis of myocardial infarction as regards diseases involving severe stress but may be of aid as regards uncomplicated angina pectoris.

SHUMAN

Bauer, F. K., Mugler, F. R., Jr., Lieberman, V. W., and Westergart, J. P.: Clearance of Radioactive Iodine from the Lower Extremities of Patients with Myocardial Infarction. Am. J. M. Sc. **232:** 44 (July), 1956.

Tracer amounts of I^{131} in normal saline, ranging from 0.5 to 1.0 microcurie, were injected by hypospray into the thighs of 35 patients with acute myocardial infarction. The rate of disappearance of the radioactive tracer was recorded either until half the radioactivity had disappeared or for a period of 30 to 60 minutes. In healthy control subjects, the disappearance of half the tracer was achieved in a mean time of 9 minutes. In those with myocardial infarction, greatly prolonged clearance times were observed during the first few weeks of illness. The clearances became normal in the sixth week in the majority of patients. It was noted that, in a number of patients, the I^{131} clearance remained prolonged in the sitting position after having become normal in the supine position. This finding may be attributable to a decrease in cardiac output in the sitting position. The mechanism of delayed clearance of tracer amounts of I^{131} in patients with myocardial infarction may be that of a diminution of the peripheral capillary bed.

SHUMAN

Cleempoel, H., and Enderle, J.: Prognostic Factors in Recent Myocardial Infarction. Acta cardiol. **9:** 260 (Fasc. 3), 1956.

One hundred and sixty-five cases of recent myocardial infarction were analyzed as to history, symptoms, and signs and evaluated according to the point system proposed by Schnur. The following were found to represent factors with unfavorable prognostic significance: advanced age, female sex, shock, congestive failure, azotemia of more than 60 mg. per cent, disturbances of rhythm, thromboembolic accidents, and a previous myocardial infarct. Diabetes and hypertension, according to this study, are not important in prognosis.

PICK

Levy, H.: The Natural History of Changing Patterns of Angina Pectoris. Ann. Int. Med. **44:** 1123 (June), 1956.

In states of coronary insufficiency that are suspected of being a prelude to coronary thrombosis, anticoagulation is now being applied with seeming success to forestall intravascular thrombosis with secondary myocardial infarction. It is important, therefore, to attempt to predict oncoming myocardial infarction in patients with known coronary disease. It is believed that such prediction is possible when changes in the pain pattern supervene or when certain new symptoms appear. In those patients in whom there is a distinct crescendo in the frequency and intensity of anginal attacks, and where there is gradual broadening of the site of radiation with the development of sweating and often vomiting, and where attacks have become quite severe and frequent, major myocardial necrosis is very likely to occur within a matter of hours or days. Significant of oncoming myocardial infarction is pain which previously brought on with some regularity by a certain degree of effort or emotion becomes provoked more quickly and with greater frequency and intensity by the same precipitant. More important is pain, previously occurring on effort, that now appears at rest and most dramatically occurs in the early hours of the morning, awakens the patient, persists for a long time, and is not relieved by glyceryl trinitrate.

WENDKOS

Aravenis, C., and Luisada, A. A.: Results of Treatment of Angina Pectoris with Choline Theophyllinate by the Double-Blind Method. Ann. Int. Med. **44:** 1111 (June), 1956.

Choline theophyllinate was tried in 72 ambulatory patients with angina pectoris. Forty-two cases received the drug, while 28 received a placebo. Neither the patient nor the doctor knew whether the drug or the placebo was used (double-blind method). The results proved that, in the majority of cases, no suggestive influence was involved in the results. No sedative effect was ascertained and tolerance was good.

The clinical improvement resulting from the drug was remarkable but gradual in its onset. It was revealed by a decrease in the number of the attacks of pain and in their severity, as well as in the partial or total discontinuance of nitroglycerin. Working capacity and the ability to walk without pain were also increased.

The electrocardiogram at rest improved only in a few exceptional cases. The electrocardiogram recorded after a 2-step test was usually comparable to that recorded prior to therapy. However, this apparent lack of change was due to the fact that most patients were unable to complete the test before therapy but could complete it afterwards. When the number of steps in the tests before and after treatment were identical, no changes followed exertion after therapy in some cases, in contrast with the deterioration of the tracing produced by exertion before therapy. This represented an objective evidence of the effect of the drug.

It is concluded that the effects of the drug are not due to its vasodilating action. It is probably due to an action on the enzyme systems of the myocardium or to the local neutralization of pressor amines that interfere with oxygen utilization in the myocardium.

WENDKOS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Wang, K. C., and Howland, W. S.: The Ballistocardiogram: Aid in Evaluation of Anesthetic and Surgical Risk. Anesthesiology **17:** 578 (July–Aug.), 1956.

The authors report a comparative study of the preoperative cardiac examination in 184 unselected patients with cancer scheduled for major surgery. The evaluation of these patients by the ballistocardiogram was compared with that obtained by the history, physical examination, and electrocardiogram. Mortality and morbidity were higher among patients showing abnormal ballistocardiograms. The results indicate that the ballistocardiogram may be a valuable tool in the preoperative evaluation of myocardial function, for it appeared to be more sensitive than the history and physical examination in detecting a cardiac abnormality, which might adversely affect the postoperative course.

SAGALL

Young, E., Wolff, L., and Chatfield, J.: The Normal Vectorcardiogram. I. Am. Heart J. **51:** 713 (May), 1956.

This report deals with a description of the normal vectorcardiogram based on vectorcardiograms and electrocardiograms taken on 100 healthy patients with normal hearts (14 women and 86 men). The Trihedron reference system was used. More than half the subjects were between 20 and 30 years of

age. The QRS$_s$Ê loop was arbitrarily divided into initial forces, body, and terminal appendage. The initial forces were defined as forces at the beginning of the QRS loop, which are oriented to the right or superior to zero. The terminal appendage was arbitrarily taken to mean the forces at the end of the QRS loop, which are oriented to the right or superiorly. The body usually appeared as a hemioval projection in the horizontal and sagittal planes, and was composed of a centrifugal and centripetal limb joining the initial forces and the appendage. The body had a leftward and inferior position and usually was oriented both anteriorly and posteriorly, rarely entirely anteriorly. A detailed study is given of the general morphology, position, and magnitude of QRS and T vectors, their direction and speed of inscription, the interrelations of various portions of the QRS loop, and of the latter to the T loop. The results by the method of analysis used in this series of normal subjects have been tested against the vectorcardiograms as found in right and left ventricular hypertrophy, myocardial infarction, right and left bundle-branch block, intraventricular block, and pulmonary embolism, and have been found to constitute a valid basis for differential diagnosis.

RINZLER

Langner, P. H., Jr., and Moore, S. R.: Location of the Electrical Center of Ventricular Repolarization. Am. Heart J. **52:** 335 (Sept.), 1956.

This report deals with a method for T-wave mirror-pattern cancellation that determines the degree of dipolarity and the location of the electric center of ventricular repolarization. Two individuals, whose equivalent dipole location for ventricular depolarization had previously been determined, were studied. The authors conclude that repolarization, as well as depolarization, is dipolar in nature and that the heart acts approximately as a dipole. In 1 individual the equivalent dipole location for ventricular repolarization was 4 cm. distant from that for depolarization, but in the other the distance between these 2 centers was only 1 cm.

RINZLER

Bougas, J., Musser, B. G., and Goldberg, H.: Left Heart Catheterization. I. Clinical Methods and Applications. Am. Heart J. **52:** 359 (Sept.), 1956.

This report deals with 127 consecutive left heart catheterizations in 120 patients. Patients considered to have clinically significant lesions of the mitral and aortic valves were selected for this study and 90 per cent of these patients had subsequent cardiac surgery. Catheterization was performed through a sharp 18-gage thin-walled styletted needle, 6 inches in length. The technic of atrial puncture is described. Atrial premature systoles were frequently observed as the needle invaginated the left atrium. Polyethylene, polyvinyl, or Nylon catheters were passed through the needle. Intracardiac and intravascular pressures were measured. The complications have consisted of hemopericardium (80 per cent) of no clinical significance and requiring no specific therapy. Hemothorax occurred on 6 and pneumothorax on 3 occasions. Sudden death occurred in 1 patient 12 hours after the procedure.

RINZLER

Burch, G. E.: Selected Quantitative Applications of Digital Rheoplethysmography. Am. Heart J. **52:** 388 (Sept.), 1956.

The continuous curves of the time courses of volumes, rates, and accelerations in inflow, outflow, and differences between inflow and outflow in the digit during a single pulse cycle are amenable to various quantitative analyses. These analyses permit a better definition of digital blood flow and provide an additional approach to the study of the physiologic mechanisms responsible for the central and peripheral circulatory states in health and disease. Selected analyses are presented of more than 300 such digital rheoplethysmograms of 10 normal and abnormal subjects. Among selected analyses presented are one that simplifies a comparison of the relative proportions of total digital inflow and outflow for any segment of the pulse cycle, one that demonstrates readily the moment-to-moment lag in outflow with respect to inflow, one that describes temporally the variations in volume inflow as a percentage of total inflow, and one that may serve as a possible index of the circulatory reserve. Differences in the state of the peripheral or central portions of the circulation are readily reflected in these various curves of the rheoplethysmogram, such as those observed for the resting state, vasoconstriction, aortic valvular insufficiency, and other states discussed in this report. In general, the increase or decrease in digital inflow was essentially symmetric and proportional throughout the pulse cycle, even with extreme vasoconstriction or vasodilatation. Particularly significant exceptions were noted in some subjects with aortic valvular insufficiency. The rate of digital flow was observed to be essentially as rapid as that reported for the brain, was over 50 per cent of that reported for the liver, about one eighth of that reported for the kidney, and several times that reported for the body as a whole.

RINZLER

Honig, C. R., and Tenney, S. M.: The "Aperiodic" Ballistocardiogram as a Function of Age. Am. Heart J. **52:** 343 (Sept.), 1956.

The aperiodic ballistocardiogram has been designed with mechanical constants selected to eliminate tissue distortion. This report deals with the normal aperiodic ballistocardiogram as a function of age and uses an instrument modified from Wittern's. The records of 73 normal subjects ranging in age from 2½ to 87 years form the basis of this report. The wave form of the "aperiodic" ballistocardiogram varies with age and force direction, though the shape of the record for any single individual is a unique and highly reproducible characteristic. Progressive shift of the frontal plane vector toward

he transverse axis of the body begins at approxmately age 40. Bidirectional recordings are thereore essential in the age group of primary clinical nterest. Respiratory variation cannot be explained on the basis of change in force direction. Though reversed respiratory variation is highly significant in subjects under 40, it may be entirely normal beyond age 50. The most important fact elucidated by this study is that reaction force remains constant throughout adult life. The hemodynamic alterations responsible for constant force output despite progressive decrease in stroke volume and contractility are discussed. Although the "aperiodic" ballistocardiogram has proved to be a valuable clinical and investigative tool, the complexity of instrumentation and interpretation precludes its use as a "service" diagnostic procedure in its present state of development.

RINZLER

Gardberg, M., and Levy, L., II: The QRS Complex of the Electrocardiogram in Myocardial Infarction with Remarks on Methods of Recording. Am. Heart J. **51:** 654 (May), 1956.

The authors have analyzed the electrocardiographic alterations of the QRS complex after myocardial infarction in the posterior, lateral, septal, anterior, and combined areas by the method of analysis developed and described by Gardberg and Ashman in 1943. Illustrative electrocardiograms show the effects on the QRS complex of varying positions of the heart. Since preinfarction electrocardiograms were available for all the demonstrated patterns, a comparison was made before and after infarction. The authors also point out that QRS changes resulting from myocardial infarction depend to a large extent upon the size of the involved area and its location: i.e., epicardial, endocardial, intramural, or transmural. Recognizing the distinction between the normal and pathologic electrocardiogram is frequently impossible and proper evaluation is achieved through a physiologic approach: thinking of the QRS complex of the electrocardiogram in terms of a QRS loop. The authors conclude that in the state of our knowledge of the electric phenomena concerned in electrocardiography and the variable factors of eccentricity and contour, it is desirable to continue recording electrocardiograms in the conventional manner rather than by spatial vector technics.

RINZLER

Wasserburger, R. H., and Lorenz, T. H.: The Effect of Hyperventilation and Pro-Banthine on Isolated RS-T Segment and T-Wave Abnormalities. Am. Heart J. **51:** 666 (May), 1956.

Thirty-four patients with no clinical evidence of heart disease but with electrocardiograms showing RS-T segment coving and frank T-wave inversion in the left and mid precordial leads were given a vagal blocking agent (Pro-Banthine). This resulted in prompt normalization of the electrocardiographic abnormalities. Hyperventilation, performed for 10 to 20 seconds consistently reproduced the original RS-T and T-wave changes. This hyperventilation effect was blocked, however, during the period of peak Pro-Banthine activity. It was noted that vasomotor instability, anxiety, and hypochondriasis were prominently manifested by these patients.

RINZLER

Zuckermann, R., and Ringleben, W.: Diagnostic Errors in Electrocardiography. Ztschr. Kreislaufforsch. **45:** 623 (Aug.), 1956.

The electrocardiogram of a 5-month-old infant showed inverted P, deep Q and wide, tall R waves in leads I and II, while leads V_{6r} through V_2 had RS deflections with the tallest R wave in V_2; leads V_3 to V_6 showed wide Q and tall R waves. At autopsy a single ventricle was found; the aorta originated from the anterior hypertrophic part. The atria were situated normally, with the right atrium showing greater hypertrophy. This case shows that inverted P waves in lead I do not necessarily indicate situs inversus of the atria. A second patient showed deep notching of the T wave in leads II and III, which simulated 2:1 atrioventricular block. Forced respiration caused sinus arrhythmia, which allowed recognition of the notch as belonging to the T wave.

LEPESCHKIN

Sterz, H., and Voill, F.: On Registration of the Jugular Venous Pulse. Ztschr. Kreislaufforsch. **45:** 616 (Aug.), 1956.

A capsule connected to a piezoelectric crystal is held to the neck by means of suction applied to a circular space surrounding it. Only the pulsation of superficial jugular vein affects the pressure in the internal space, so that the venous pulse registered in this way is little affected by the pulsation of the carotid artery.

LEPESCHKIN

Polzer, K., Schuhfried, F., and Heeger, H.: Venous Congestion in the Rheogram. Ztschr. Kreislaufforsch. **45:** 609 (Aug.), 1956.

The precordial rheogram (impedance plethysmogram), in the lead from the right shoulder to the heart apex, shows extreme elevation of the protodiastolic venous wave in tricuspid insufficiency. The rheogram of the arm shows a corresponding second venous wave after a conduction time of about 0.14 second. These waves are present also in cases not showing tricuspid regurgitation and are caused by a temporary increase in venous engorgement at the beginning of diastole. The venous wave in the arm disappears after ligation of the inferior vena cava. The rheogram in the lead from the right to the left jugular vein shows a systolic plateau in tricuspid regurgitation.

LEPESCHKIN

HYPERTENSION

Litin, E. M., Faucett, R. L., and Achor, R. W. P.: Depression in Hypertensive Patients Treated with *Rauwolfia serpentina*. Proc. Staff Meet., Mayo Clin. **31:** 233 (April), 1956.

The authors feel that the evidence does not support the idea that Rauwolfia per se induces a depression. It is much more likely that the effect of the medication upsets the psychologic balance upon which the patient's ability to get along with himself and others has depended all his life. This alteration seems to create a vulnerability in the patient, such that the usual stresses and strains of this age period tend to bring on a depression. The drug, apparently has a different action when used with overactive, disturbed psychotic persons than when given to tense, anxious, inhibited psychoneurotic individuals. Reports on its use in psychoneuroses are pertinent here. It apparently acts initially as a sedative without soporific action and lessens anxiety. As its use is continued, it seems to be a "deinhibitor." It is reported to free the neurotic from the constriction of his defense system, and patients report enthusiastically about their feeling of freedom. This lessening of inhibition makes the patient more likely to express real feelings of anger. If he does so however, he is immediately threatened, as he sees it, with the withdrawal of his security needs by significant people in his environment who represent the mother-figure of his childhood. Thus a depression ensues upon rather minor shifts of attitude in his interpersonal environment. A depression, it should be noted, serves as an effective defense against the expression of unacceptable angry feelings.

The authors conclude that the possible complication of depression should not preclude the use of this drug that has been shown to have beneficial effects in a large percentage of hypertensive patients. It should not, however, be used indiscriminately but only under supervision, not only to observe the effects on the blood pressure, but more particularly for any evidence of depression. There was no apparent correlation between the emotional responses to Rauwolfia and the effect on the blood pressure.

SIMON

Bello, C. T., and Turner, L. W.: Reserpine as an Antihypertensive in the Outpatient Clinic: A Double-Blind Clinical Study. Am. J. M. Sc. **232:** 194 (Aug.), 1956.

Reserpine was administered to a group of 25 hypertensive patients of which 23 were female; 17 of the entire group were Negroes. The objective studies included blood pressure readings, pulse rate, fundoscopic examinations, and electrocardiograms obtained before and during the course of treatment. The results indicated that no remarkable fluctuations in blood pressure occurred; a slight lowering of pulse rate was noted. There was some improvement in several electrocardiograms, which could not be attributed to lowering of blood pressure. Side effects were noted in approximately two thirds of the patients including muscle pains, nasal stuffiness, drowziness, headache, nausea, and vomiting. The authors conclude that the environmental factors are important in contributing to the results obtained with reserpine therapy in hypertension.

SHUMAN

Roth, G. M., and Kvale, W. F.: Pheochromocytoma, Factors in the Accurate Pharmacologic Diagnosis. Dis. of Chest. **29:** 366 (April), 1956.

The authors review the pharmacologic tests used in diagnosing pheochromocytomas, emphasizing the precautions necessary to avoid false results. In the normotensive phase a cold pressor test should always precede the histamine test, and the latter must demonstrate a rise of at least 60 mm. systolic and 40 mm. Hg diastolic to be significant. Moreover, the blood pressure rise must be substantially above that of the cold pressor test, the average difference in 19 patients being 70 mm. systolic and 19 mm. diastolic. A regitine test may be performed at the height of the blood pressure rise following histamine, and a rapid fall in blood pressure represents 2 positive tests. In the presence of sustained hypertension a regitine test of 5 mg. intravenously should yield a significant drop in blood pressure in 30 to 60 seconds, with a slow return to previous levels. Regitine should not be administered intramuscularly as false negative results occur. No sedation or narcotics should be given for 48 hours prior to these tests, as the cold pressor response may be suppressed and the response to regitine or piperoxan accentuated leading to false positive results. The authors also mention 4 reported cases of intrathoracic pheochromocytomas, in 2 of whom successful surgical procedures were carried out. Two patients with recurrent metastases from surgically removed pheochromocytomas are also discussed.

MAXWELL

Moyer, J. H., Ford, R., Dennis, E., Caplovitz, C., Hershberger, R., Conner, P. K., Kinard, S., and McConn, R.: Drug Therapy (Mecamylamine) of Hypertension. III. Results with Mecamylamine, a Completely Absorbed Ganglionic Blocking Agent. Arch. Int. Med. **98:** 187 (Aug.), 1956.

Results obtained in the treatment of hypertension with mecamylamine, a ganglionic-blocking agent, which is completely absorbed from the intestinal tract, are reviewed. The patients were treated as ambulatory patients. The drug is an effective agent for reducing the blood pressure in patients with severe hypertension. Because of its complete oral absorption, it is more predictable from day to day, and dosage is easier to titrate, since the oral and

parenteral route of administration can be used interchangeably with the same dose.

The side effects with mecamylamine are similar, both qualitatively and quantitatively, to those observed with other available ganglionic-blocking agents, such as hexamenthonium and pentolinium. The effect of reducing salivation is more marked with mecamylamine than with the other blocking agents, and the initial effect of reducing intestinal peristalsis may be more marked than with other blocking agents. The pharmacology and specific clinical problems relative to the use of this drug for the treatment of hypertension are reviewed.

BERNSTEIN

Freis, E. D., and Wilson, I. M.: Mecamylamine, a New, Orally Effective, Hypotensive Agent. Experimental and Clinical Evaluation. Arch. Int. Med. **97:** 551 (May), 1956.

Mecamylamine seems to be completely absorbed from the intestinal tract of man. The hypotensive effect began after 1 hour, reached the lowest values at 2 hours and disappeared in 6 to 12 hours. In equipotent hypotensive doses mecamylamine did not produce as marked an inhibition of sympathetic vasoconstrictor reflexes as had been observed previously with hexamethonium. In 36 patients with severe hypertension treatment with mecamylamine in an average dose of 29 mg. per day was followed by a mean reduction in blood pressure of 21 per cent systolic and 16 per cent diastolic in the supine position and 25 per cent systolic and 20 per cent diastolic in the erect position.

Continuous treatment for 1 to 4 months frequently resulted in improvement in the optic fundi and occasionally in the electrocardiographic patterns. A decrease in blood urea nitrogen levels also was noted in most patients exhibiting slight elevations but not in those with marked nitrogen retention. The side effects were typical of those experienced with other ganglion-blocking agents. In the majority of patients the development of "tolerance" was slight or nonexistent. The addition of small doses of hydralazine appeared to produce a slight additional hypotensive effect in 3 of 13 patients. Reserpine seemed to produce an additional hypotensive effect in 5 of 11 patients.

BERNSTEIN

METABOLIC EFFECTS ON CIRCULATION

Kreuziger, H., Kemper, F., and Heinecker, R.: The Effect of Cigarette Smoking on the Blood Composition. Ztschr. Kreislaufforsch. **45:** 167 (Mar.), 1956.

In 21 normal young persons accustomed to smoking, inhaling the smoke of 1 cigarette caused in all cases an increase of leukocyte concentration and decrease of eosinophils. In most cases the neutrophils increased and blood sugar showed an initial decrease, with later increase, while the potassium concentration decreased. In a minority of cases the lymphocytes, the blood sugar, and the serum potassium showed an immediate elevation. Five anesthetized dogs behaved like the majority of human subjects. The serum sodium and calcium were not affected.

LEPESCHKIN

Follis, R. H., Jr.: The Effects of Nutritional Deficiency on the Heart: A Review. Am. J. Clin. Nutrition **4:** 107 (Mar.–Apr.), 1956.

In this review article the author discusses the cardiac changes (physiologic and anatomic alterations) that have been produced in the experimental animal by deficiencies of various inorganic elements, amino acids, vitamins, and fatty acids. The application of these findings to an understanding of the changes seen in human beings with nutritional deficiencies are indicated.

SAGALL

Emele, J. F., and Bonnycastle, D. D.: Cardiotonic Activity of Some Adrenal Steroids. Am. J. Physiol. **185:** 103 (Apr.), 1956.

Small concentrations of compounds B, F, E, and S have a positive inotropic effect on hypodynamic cat papillary muscles. Higher concentrations of these and all concentrations of DCA and compound A depress papillary muscle. Ten per cent serum, 1 per cent serum albumin, and a dialysate of 1 per cent albumin are all positively inotropic. The steroids did not account for this positive action.

OPPENHEIMER

Horwitt, M. K., Harvey, C. C., Duncan, G. D., and Wilson, W. C.: Effects of Limited Tocopherol Intake in Man with Relationships to Erythrocyte Hemolysis and Lipid Oxidations. Am. J. Clin. Nutrition **4:** 408 (July–Aug.), 1956.

The organization of a project designed to evaluate man's requirement for vitamin E was described. This project is still in progress. Quantitative tests included evaluation of creatine, creatinine, nitrogen, pentose, and a rough estimation of amino acid distribution in urine. Plasma was analyzed for tocopherol content, total fatty acids, linoleic, linolenic, and arachidonic acids, cholesterol, vitamin A, and carotenoid substances. Hemograms, liver function studies, tolerance curves for glucose, lactic acid, and pyruvic acid were obtained. Clinical and physiologic procedures included the Master test, electrocardiograms, circulation time, Rumpl-Leede fragility test, skin-fold caliper measurements, basal metabolic rate, and electromyogram base lines. No significant variations in any of these tests other than the changes in plasma tocopherol and the susceptibility of the erythrocytes to hemolysis by hydrogen peroxide were demonstrated. It was

suggested that variables other than the concentration of alpha-tocopherol in the blood are involved in hemolysis. Erythrocyte hemolysis by hydrogen peroxide has been related to oxidation of the lipoid structure of the red blood cell by comparing data obtained from the oxidation of linolenic acid, phospholipids, and brain lipids with oxidations of erythrocyte lipids. Thiobarbituric acid (TBA) had been suggested as a suitable reagent for evaluating the oxidation of biological material in studies of vitamin E deficiency. With this reagent, data have been obtained that show an increased reactivity with biological material from mammals depleted of vitamin E. Correlations between TBA reactivity and the extent of peroxide hemolysis in human erythrocytes were observed.

MAXWELL

PHARMACOLOGY

Jaffe, H. L., Rosenfield, M. H., Pobira, F. W., and Stuppy, L. J.: Radioiodine Treatment of Euthyroid Cardiac Disease. J. A. M. A. **159:** 434 (Oct. 1), 1955. Abstracted, Circulation **15:** 266 (Feb.), 1957.

Okita, G. T., Talso, P. J., Curry, J. H., Jr., Smith, F. D., Jr., and Geiling, E. M. K.: Metabolic Fate of Radioactive Digitoxin in Human Subjects. J. Pharmacol. & Exper. Therap. **115:** 371 (Dec.), 1955. Abstracted, Circulation **15:** 224 (Feb.), 1957.

Roddie, I. C., Shepherd, J. T., and Whelan, R. F.: The Action of 5-Hydroxytryptamine (5-HT) on the Blood Vessels of the Human Hand and Forearm. Brit. J. Pharmacol. **10:** 445 (Dec.), 1955. Abstracted, Circulation **15:** 273 (Feb.), 1957.

Storstein, O., and Tveten, H.: Quinidine Treatment of Established Auricular Fibrillation. Acta med. scandinav. **153:** 57 (Dec. 16), 1955. Abstracted, Circulation **15:** 13 (Jan.), 1957.

Lasagna, L.: Drug Effects as Modified by Aging. J. Chron. Dis. **3:** 567 (June), 1956.

Although chronologic age has been shown to be correlated with response to drugs in certain circumstances, such correlation is not inevitable nor is its nature predictable. At times increasing age seems to predispose to hyperreactivity, at times to hyporeactivity, and at times seems not to affect the magnitude of response. The problems involved in establishing and assessing such correlations are discussed. Some points touched upon were computation of drug dosage for a given age on the basis of grams per square meter of body surface, or on the basis of body weight, or square root of body weight; the problem of accounting for possible variation in distribution and metabolism of a given drug for different age groups; variation in the shape of the dose-response curve of a particular drug in a specific age group. It is suggested that the systematic collection of data bearing on these problems may provide leads for important contributions to our understanding of the fate and action of drugs.

MAXWELL

Petermann, A., and Schultz, G. W.: Clinical Study on the Action of Beta-Pyridylcarbinol (Ronicol) on the Heart and Circulation. Ztschr. Kreislaufforsch. **45:** 284 (Apr.), 1956.

Intravenous injection of 100 mg. in 12 normal persons usually caused a decrease of blood pressure, little change in heart rate, decreased stroke and minute volume, and increased peripheral resistance (calculated according to Broemser and Ranke). In 12 persons with cardiovascular disease the blood pressure and the minute volume usually increased, while the peripheral resistance decreased. These changes were often followed by a reaction in the opposite sense.

LEPESCHKIN

Castellanos, A., Jr., Azan Cano, L., and Taquechel, N.: The Clinical Use of Acetyl Strophanthidin. Rev. Cubana cardiol. **16:** 483 (Dec.), 1955.

In persons who had previously received no digitalis, 0.2 mg. of the drug was injected intravenously every 5 minutes, followed by electrocardiographic registration, until a total of 1.8 mg. was reached or signs of toxicity appeared. In persons previously on digitalis, 0.2 mg. was injected every 10 minutes in the same way. In 10 patients with normal hearts no significant changes of S-T or Q-T appeared. In 15 cardiac patients without previous digitalis these changes appeared more readily; up to 1.8 mg. was necessary to cause slowing in atrial fibrillation. Twenty-five cardiac patients treated with digitalis occasionally showed ventricular bigeminy and tachycardia after only 0.2 mg. of acetyl strophanthidin; however, in some cases these did not become more numerous on further injection of the drug. In 6 cases, atrial tachycardia with variable atrioventricular block appeared, and in 2 of these it evolved into atrial fibrillation. When this tachycardia was a result of digitalis intoxication, acetyl strophanthidin caused an increase in atrial rate, complete atrioventricular block with ventricular bigeminy, and sometimes atrial fibrillation. On the contrary, in 3 cases where this tachycardia appeared without previous digitalization, acetyl strophanthidin caused sinus rhythm to appear after 1.2 to 1.8 mg. In 1 case with bilateral bronchopneumonia with sinus tachycardia and coupled ventricular extrasystoles, 1.2 mg. of the drug caused these to disappear, but after 3 minutes ventricular tachycardia and fibrillation appeared, leading to death. Intravenous infusion of 50 to 75 mEq. of potassium in 20 to 180 min. always caused ectopic rhythms due to digitalis to disappear during or after the infusion; the atrial rate of atrial tachycardia showed a progressive slowing with transition to 1:1 conduction before sinus rhythm appeared. Procaine amide always caused ventricular extrasystoles to disappear in doses less than 500 mg., atrial paroxysmal tachycardia due to digitalis or acetyl strophanthidin (sometimes at rates up to 310) was converted to sinus rhythm as in the case of potassium

in the majority of the cases, but in 4 cases only slowing of the atrial rate resulted, and in 1 of these 1:1 conduction with marked widening of QRS appeared. Usually a shortening of P-R accompanied the slowing of the tachycardia. Potassium is accordingly preferred in the treatment of atrial arrhythmias, while procaine amide is preferred in that of ventricular arrhythmias because of a more rapid action. In general, acetyl strophanthidin is not more toxic than other intravenous digitalis preparations if the intervals between injections exceed 10 min.

LEPESCHKIN

Jerzy Glass, G. B., Baronsky, H., Boyd, L. J., Rich, M., and Ebin, L.: Theophylline Concentration in Blood Plasma Following Rectal Administration of Aminophylline. Am. J. M. Sc. **231:** 51 (Jan.), 1956.

Aminophylline was administered as a suppository to 30 subjects to evaluate the efficiency of this mode of therapy and to determine the best suited suppository bases for this purpose. Plasma levels of theophylline were measured for a period of 1 to 8 hours using the Schack-Waxler ultraviolet spectrophotometric method. The plasma levels obtained after intrarectal administration of aminophylline were checked against blanks obtained from blood obtained before administration. Placebo suppositories were also employed as controls for the observations. The results demonstrated that 2 types of suppositories gave satisfactory blood levels of theophylline. The first of these contained 0.5 Gm. of aminophylline in a mannitol base, with or without benzocaine. The plasma levels of theophylline were over 500 μg. per 100 ml. in 8 of 10 tests. The second type of suppository was that in a buffered carbowax base, which produced similar levels in 4 of 6 subjects. Sustained plasma levels of theophylline averaging 650 μg. per 100 ml. between the fourth and eighth hours and with the least coefficient of variation were achieved with the mannitol base suppositories. Intravenous aminophylline given to 2 subjects in 0.5 Gm. doses resulted in blood levels approximately 3 times higher than that obtained with the same dose in the suppository form with blood levels well maintained for 2 to 3 hours after injection.

SHUMAN

Purpura, D. P., and Grundfest, H.: Blockade of Cardiac Synapses by Succinylcholine. Science **124:** 319 (Aug. 17), 1956.

A reversible cardiac synaptic blockade was induced by succinylcholine in anesthetized cats and in unanesthetized spinal preparations.

Succinylcholine is a cholinomimetic agent that acts like acetylcholine to depolarize muscle endplates prior to blocking neuromuscular transmission. Its blockade of vagal effects resembles the action of nicotine when the latter is given slowly in low concentration. In neither case was a slowing of the heart observed, such as occurs with larger doses of nicotine or with injections of acetylcholine. Therefore, the vagal blockade caused by succinylcholine is ascribed by the authors to depolarizing blockade of transmission from the preganglionic vagus to the intracardiac postganglionic parasympathetic fibers.

WAIFE

PHYSIOLOGY

Carlill, S. D., and Duke, H. N.: Pulmonary Vascular Changes in Respone to Variations in Left Auricular Pressure. J. Physiol. **133:** 275 (Aug.), 1956.

It has been asserted by other investigators that elevation of left atrial pressure (as in mitral stenosis) causes a greater increase in pulmonary arterial pressure due to pulmonary arteriolar constriction. This mechanism was not demonstrable in the perfused lung of cats. As a matter of fact, a rise in left atrial pressure caused a reduction in pulmonary vascular resistance and an increase in blood volume in the lungs.

AVIADO

Lilienfield, L. S., and Kovach, R. D.: Simplified Method for Calculating Flow, Mean Circulation Time and Downslope from Indicator-Dilution Curves. Proc. Soc. Exper. Biol. & Med. **91:** 595 (Apr.), 1956.

The use of indicator-dilution curves to measure cardiac output and "central blood volume" is time consuming when the curves are markedly prolonged as in heart failure. A new graphic method using semilogarithmic paper is described and its validity is supported by mathematical proof. The advantages of employing this method of calculation include speed and accuracy.

AVIADO

Douglas, W. W., Ritchie, J. M., and Schaumann W.: Depressor Reflexes from Medullated and Non-Medullated Fibers in the Rabbit's Aortic Nerve. J. Physiol. **132:** 187 (Apr.), 1956.

Experiments were made in which the action potentials set up in the rabbit's aortic nerve by electric stimulation were correlated with their reflex depressor effects. In addition to the medullated afferent depressor fibers (A fibers) known to be arising from the aortic baroreceptors, the aortic nerve contains a large group of small nonmedullated afferent fibers (C fibers) with powerful reflex depressor activity. The origin of these C fibers is unknown but the possibility of their participation in reflex effects from the heart and lungs is discussed.

AVIADO

Meesman, W., and Schmier, J.: Cardiac and Circulatory Defects of Body Substances Compared to those of the "Spleno-Hepatic Mechanism." Ztschr. Kreislaufforsch. **45:** 335 (May), 1956.

Electric stimulation of the splenic nerves after constriction of the descending coronary artery causes elevation of the blood pressure and heart output, accompanied by decreased flow in the right coronary artery. This decrease in flow is not followed by a compensatory increase and is interpreted as due to a primary decrease in the oxygen consumption of the myocardium, which counteracts anoxia. The flow in the hepatic artery is increased preceding the increase in arterial pressure. The effect on the heart is attributed to liberation of Rein's "hypoxy-lienin" by spleen and liver. After injection into the femoral or hepatic veins of ferritin, levulose, glucose, lactic acid, potassium, adenosine triphosphoric, diphosporic and monophosphoric acids, serotonin creatine sulfate, and extracts of the spleen and liver, an increase in the coronary flow appeared. It is therefore concluded that none of the above substances can be responsible for the effect of splenic nerve stimulation, since the latter causes decreased coronary flow. Previously it could be shown that epinephrine and norepinephrine also cannot be responsible for this effect.

LEPESCHKIN

Maurea, C., Nylin, G., and Sollberger, A.: Normal Values of the Nylin Heart Function Test. Acta. cardiol. **11:** 215 (Fasc. 3), 1956.

Following a review of Nylin's previous investigations, the authors present a statistical analysis of results of cardiopulmonary function tests obtained in 763 normal persons aged from 15 to 60 years. The following factors were taken into consideration: age, weight, height, body surface, Benedict's standard values, oxygen consumption at rest and after exercise, oxygen debt, cardiac volume per square meter of body surface, and the basal metabolic rate. Mean values were tabulated for men and women and frequency diagrams were reproduced. The correlations between observed and calculated oxygen consumptions are discussed. The former correlated well with heart volume but not with age. No relation could be established between oxygen debts and age, length, weight, body surface, basal metabolic rate, or heart volume. Possible errors influencing the statistical evaluation are discussed. Nomograms of correlations between exercise and resting oxygen consumption for practical use are presented.

PICK

Gobbato, F., and Meda, A.: Analysis of Factors That May Influence the Duration of Isotonic Systole in Normal Conditions. Cardiologia **29:** 114 (Fasc. 2), 1956.

In 84 patients aged 28 to 89 years, without symptoms or signs of cardiovascular disease, the duration of the ventricular ejection phase ("isotonic systole") was determined and correlated with the ventricular rate, the stroke output, blood pressure, peripheral resistance, and elasticity of the arteries. The respective data were determined from simultaneous recordings of carotid and femoral pulses by Frank's (air transmission) sphygomograph. The stroke output was calculated according to Wezler and Böger and as a measure of arterial elasticity the velocity of the pulse wave was taken into consideration. The data were analyzed statistically and respective regression formulas were presented. The conclusion was reached that in normal individuals, regardless of age, the duration of the ventricular ejection phase depended at rest on the heart rate and stroke output and was unaffected by variations of the blood pressure, by the peripheral resistance, and by elasticity of the arteries as occurred with advancing age. A nomogram was presented that may be useful in the evaluation of alterations of the ejection phase under abnormal conditions.

PICK

Cull, T. E., Scibetta, M. P., and Selkurt, E. E.: Arterial Inflow into the Mesenteric and Hepatic Vascular Circuits During Hemorrhagic Shock. Am. J. Physiol. **185:** 365 (May), 1956.

Both mesenteric and hepatic arteries were observed to have decreased blood flows during hemorrhagic shock. Resistance increased in the hepatic artery. At the latter end of a period of low blood pressure, mesenteric arterial resistance often decreased at the same time during which there was an elevation in venous portal pressure. Hepatic arterial resistance continued to increase during this same late hypotensive period. Transfusion increased mesenteric blood flow. These values were often above the original control values. At the same time portal pressures increased 2 fold while mesenteric resistance decreased. It is suggested that this phase may represent mesenteric pooling in capillaries and venules depending on reduced inflow and increased outflow resistance. Later mesenteric resistance increased up until the agonal period. There was sometimes a terminal decrease. Hepatic artery flow increased gradually after transfusion. The maximum was at 90 minutes. At this time mesenteric artery flow was very much reduced with an extremely high resistance.

OPPENHEIMER

Laurent, D., Bolene-Williams, C., Williams, F. L., and Katz, L. N.: Effects of Heart Rate on Coronary Flow and Cardiac Oxygen Consumption. Am. J. Physiol. **185:** 355 (May), 1956.

At rates up to 300 beats per minute there was a significant correlation with coronary flow and cardiac oxygen use. The role of rate in the determination of cardiac oxygen utilization is stressed. When rates were excessive or the load was very great the relationship of coronary flow to oxygen consumption was shifted. Under these conditions energy metabo-

lism of the heart changed so that less oxygen was extracted from blood even though it was more available. Anaerobic activity of the heart may therefore have a definite role for periods that are long enough to exclude ordinary oxygen debt.

OPPENHEIMER

Hearn, G. R., and Wainio, W. W.: Succinic Dehydrogenase Activity of the Heart and Skeletal Muscle of Exercised Rats. Am. J. Physiol. **185:** 348 (May), 1956.

Rats were allowed to swim for ½ hour daily up to 5 to 8 weeks. Exercised rats did not gain as much weight as controls. Adrenal glands and ventricular weights were increased in the exercised animals. There was no change in skeletal muscles in these same rats. The relative total succinic dehydrogenase activity was significantly increased in heart ventricle but not in gastrocnemii. Unit and actual total activities were not changed in either skeletal or heart muscle.

OPPENHEIMER

Mooring, P. K., Rathe, J., and Root, W. S.: Pressor Response to Adrenalin Shown by Spinal Dogs. Am. J. Physiol. **186:** 85 (July), 1956.

Under anesthesia vagotomized dogs, whether or not carotid sinuses were denervated, responded to intravenous epenephrine in a manner similar to control animals. Low cervical section of the cord, however, was attended by a 3-fold increase in response to epinephrine under anesthesia. When vagotomy was added, the response was still greater. If cord section was made 1 or 2 segments below C_8 to T_1, the epinephrine response was reduced. Anesthetized spinal dogs (C_8 to T_1) were more responsive to epinephrine than similar unanesthetized animals.

OPPENHEIMER

Lammerant, J., and DeVisscher, M.: Determination of Mean Pulmonary Circulation Time by Radiocardiography. Acta cardiol. **11:** 244, 1956.

The intracardiac transport of human serum albumin labeled by I^{131} was determined with the help of a scintillation counter directed toward the precordium. Fluctuations of the intracardiac radioactivity were registered as a function of time in the form of 2 successive and partly superimposed concentration curves. The curves were produced by the right and left heart respectively and permitted measurement of the mean circulation time of the tracer substances through the lungs. The method was useful in determination of the circulating lung blood volume, since it eliminated extrapulmonary factors involved in conventional dye-dilution technics. The technic of the method is described in detail, and the significance of the measurable mean lung circulation time is discussed.

PICK

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Epstein, F. H., Kleeman, C. R., Lamdin, E., and Rubini, M. E.: Studies of the Antidiuresis of Quiet Standing: Observations upon Electrolyte and Acid-Base Excretion during Sulfate Diuresis. J. Clin. Invest. **35:** 308 (March), 1956.

The effects of motionless standing on electrolyte metabolism were determined in normal young men. When isotonic sodium sulfate was infused, there was an abrupt decrease in renal excretion of sodium and chloride, but little change in urine flow or sulfate excretion. There was also an increase in potassium and ammonium excretion, and a fall in urinary pH. Administration of Diamox, prior to quiet standing, prevented the increased potassium excretion. Thiomerin also blocked the increase in potassium excretion, but did not prevent the formation of a more acid urine and an increase in ammonium excretion. These results demonstrate that changing from the supine to the standing posture provides a specific stimulus to the renal tubular reabsorption of sodium. The data are compatible with the theory that the renal retention of sodium so produced, is caused in part by an increased reabsorption of sodium from urine through ionic exchange with the tubular cells for potassium and hydrogen ions.

WAIFE

Hickam, J. B., Wilson, W. P., and Frayser, R.: Observations on the Early Elevation of Serum Potassium during Respiratory Alkalosis. J. Clin. Invest. **35:** 601 (June), 1956.

A transient hyperkalemia was induced by hyperventilation in normal subjects when acute respiratory alkalosis was reached. Early in respiratory alkalosis, potassium was added to the circulating blood from the splanchnic region, and was removed from the blood in the brain and peripheral tissue. Later the serum potassium concentration fell below resting levels as potassium moved from an extracellular to an intracellular position.

WAIFE

Preedy, J. R. K., and Aitken, E. H.: The Effect of Estrogen on Water and Electrolyte Metabolism. III. Cardiac and Renal Disease. J. Clin. Invest. **35:** 443 (Apr.), 1956.

In patients with constrictive pericarditis, estrogen administration was associated with marked and sustained retention of water, sodium, and chloride. Similar though less striking effects were noted in patients with congestive heart failure. In normal subjects slight and transient effects only were observed.

However, in patients with the nephrotic syndrome, significant retention of salt and water was not found. This would suggest that the kidney plays no primary role in such retention. The only factor common to all groups in which fluid retention after estrogen

occurred, and absent from groups in which retention did not occur, was hepatic involvement. Strong support is provided for the hypothesis that differing degrees of hepatic circulatory impairment lead to differing rates of estrogen inactivation and may be responsible for the marked fluid retention after estrogens in cirrhosis with ascites in contrast to the slight retention in cirrhosis without ascites.

WAIFE

Mulrow, P. J., Oestreich, H. M., and Swan, R. C.: Measurement of Extracellular Fluid Volume of Nephrectomized Dogs with Mannitol, Sucrose, Thiosulfate and Radiosulfate. Am. J. Physiol. **185:** 179 (April), 1956.

Distribution volumes of mannitol, sucrose, thiosulfate, and radiosulfate were unchanged in extracellular fluid 6 hours after removal of both kidneys

OPPENHEIMER

Little, J. M., Kelsey, W. M., and Yount, E. H., Jr.: Influence of the Adrenal Cortex on Renal Hemodynamics in the Dog. Am. J. Physiol. **185:** 159 (April), 1956.

Atrophic changes in the zona reticularis and fasciculata of the adrenal cortex were produced by Rhothane. ACTH increased the glomerular filtration rate and the effective renal plasma flow, but decreased the filtration fraction. Rhothane decreased renal function in 60 per cent of the dogs and ACTH restored all parameters except the filtration fraction. If Rhothane and ACTH were administered at the same time a progressive decrease in function resulted in animals with elevated levels (3 out of 5 dogs).

OPPENHEIMER

Knowles, H. C., Jr., and Alverson, G.: The Osmotic Activity of the Renal Tubule in Diabetic Acidosis. J. Lab. & Clin. Med. **48:** 176 (Aug.), 1956.

Data were reported dealing with the relations of urinary flow, osmolarity, and load in patients with ketoacidosis. Observations made on 19 subjects with diabetic acidosis revealed no correlation between urinary total osmolarity and flow and the fact that osmotic activity is minimally diminished in the uncomplicated case. Granting that the data were few, they suggested some diminution of distal tubular water reabsorption in acidosis. It appeared that uncomplicated moderate ketoacidosis caused only minimal impairment of concentrating ability. It was suggested that factors such as potassium deficiency or renal ischemia may alter tubular function. However, from the data reported it was apparent that the concentrating ability of the kidney was appreciably decreased only when hypotension or other complication was present. The flow is closely related to the total load and to glucose load as well, since glucose comprises the largest and a relatively constant fraction (40 per cent) of the load.

MAXWELL

ROENTGENOLOGY

Broman, T., and Olsson, O.: Technique for the Pharmaco-Dynamic Investigation of Contrast Media for Cerebral Angiography. Acta radiol. **45:** 96 (Feb.), 1956.

In this as in previous articles the authors report on their investigations of the blood-brain barriers, to indicate the roles played by concentration of the opacifying media, and the importance of the injection pressure. In this study a 35 per cent solution of Umbradil was injected into the carotid artery (rabbits), under conditions varying in amount, time, and recorded pressures, and the resultant effects on brain tissue were assayed. While the duration of injection and the pressures employed by themselves were not determining factors in producing brain damage the cumulative effects of both these factors combined led to significant brain injury.

The authors conclude that in clinical cerebral angiography the injection pressure probably plays only a minor role unless on theoretic grounds it is performed in patients with arterial hypertension, when undesirable effects might result.

SCHWEDEL

Falomir, J. M., and Sepulveda, B.: Splenoportography for the Diagnosis of Portal Hypertension. Arch. Int. Med. **98:** 42 (July), 1956.

Percutaneous splenoportography is a safe and diagnostically valuable procedure, as evidenced by the series of cases presented in this paper. The chief usefulness of the method rests with its ability to offer the following information: (1) confirmation of the existence of portal hypertension, (2) localization of the site of obstruction, and (3) demonstration of anomalies of the portal system. The authors believe that with increasing application of this procedure more complete understanding of the portal circulation will be possible.

The contraindications for splenoportography are pronounced tendency to hemorrhage, infectious splenomegaly, and the presence of ascites, which must be aspirated prior to attempting visualization.

BERNSTEIN

Figley, M. M., Nordenström, B., Stern, A. M., and Sloan, H.: Angiocardiographic Mixing Defects as Indicators of Left to Right Shunts. Acta radiol. **45:** 425 (June), 1956.

Angiocardiograms in 75 patients with verified left-to-right shunts were reviewed. Patients with patent ductus arteriosus showed nonopacified filling defects demonstrable either at the venous

end of the ductus or extending proximally almost to the pulmonic valve. These occurred almost always in ventricular diastole, less frequently in systole. In patients with ventricular septal defects mixing defects, large or small, oftener in systole than diastole were demonstrated in 7 of 18 cases. With atrial septal defect findings were diagnostic only within sharply marginated right atria in 3 of 13 cases. There was 1 demonstrable instance of total pulmonary venous drainage into a left superior vena cava draining into a left innominate vein and another with indentation of the lateral margin of the superior vena cava by a right anomalously draining pulmonary vein.

SCHWEDEL

Bétoulières, P., Giraud, G., Pélissier, M., Barjon, P., Latour, H., and Puech, P.: Combined use of Simultaneous Polytomography and Angiocardiograph in the Analytical Study of Cardiac and Vascular Cavities. Arch. mal. coeur **49:** 441 (May), 1956.

In rabbits a deep cassette containing 6 films 8 mm. apart is swung manually during injection of radiopaque dye. In order to compensate for the different intensity of the x-rays falling on each film, the more distant films have stronger intensifier screens and are developed longer. The 6 roentgenologic cross-sections of the heart obtained by this method allow recognition of the cardiac cavities, great vessels, and valves with much greater clarity than conventional angiocardiography. Technical improvements will allow the reduction of the swing time to less than 0.1 second and its synchronization with the electrocardiogram, so that systolic and diastolic tomograms can be obtained.

LEPESCHKIN

SURGERY AND CARDIOVASCULAR DISEASE

Kruse, C. A., and Kirby, F. G.: Maximum Benefit from Thromboendarterectomy. J.A.M.A. **161:** 324 (May 26), 1956.

Recent surgical literature indicates an increasing acceptance of the direct surgical treatment of obstructive arteriosclerosis. The removal of the obstruction and the reestablishment of the vascular channel by resection and replacement by a suitable vascular graft, or by thromboendarterectomy have both been successful. A case of obstructive arteriosclerosis of the right common iliac artery treated by thromboendarterectomy is reported. Maximum benefit was obtained and this benefit has been maintained over a period of 3 years, suggesting that the vessel will remain patent for the duration of the patient's life and that this area will be the least involved by future arteriosclerotic changes in his total vascular system. Selection of patients with localized or segmental arteriosclerosis and well-developed collateral circulation would seem to be the greatest factor in obtaining a maximum result by thromboendarterectomy.

KITCHELL

Glenn, W. W. L., Bloomer, W. E., and Spear, H. C.: Operative Closure of the Patent Ductus Arteriosus: A Report of 110 Operations without Mortality. Ann. Surg. **143:** 471 (April), 1956.

The authors described their experiences in the surgical closure of a patent ductus arteriosus in a series of 110 operations, performed on patients ranging in age from 7 months to 42 years. In 91 patients the ductus was divided between Potts ductus clamps. In every patient 1 or more antibiotics were given. All patients survived. The authors did not think that division of the ductus was more hazardous than ligation. They pointed out that for the best results in the treatment of this condition, the surgeon, pediatric or medical cardiologist, anesthetist, and radiologist must work together as a team.

ABRAMSON

Baffes, T. G.: A New Method for Surgical Correction of Transposition of the Aorta and Pulmonary Artery. Surg., Gynec. & Obst. **102:** 227 (Feb.), 1956.

After attempting various procedures for the correction of transposition of the aorta and pulmonary artery, the author found most satisfactory the technic of utilizing a homologous aortic graft to transpose the inferior vena cava and the right pulmonary veins. This approach was applied successfully in 1 patient.

The operation consisted of dissecting the right pulmonary veins and the inferior vena cava free and applying a curved coaretation clamp on the latter vessel so that blood flow through it into the right atrium was not occluded. An incision was made in the portion of inferior vena cava held within the coaretation clamp and one end of the aortic graft was anastomosed to the edges of the incision. The open end of the graft was sutured to the lateral wall of the right atrium. Finally, the attachment of the inferior vena cava to the right atrium was divided, causing blood to flow from the inferior vena cava through the aortic graft and into the left atrium. With such a procedure, blood from the inferior vena cava empties into the pulmonary circulation via the left atrium, while blood from the right pulmonary veins reaches the systemic circulation by way of the right atrium.

ABRAMSON

Dale, W. A., Pualwan, F., and Bauer, F. M.: Ligation of the Inferior Vena Cava with Absorbable Gut. Surg., Gynec. & Obst. **102:** 517 (May), 1956.

Temporary ligation of the inferior vena cava was

performed in 55 dogs using absorbable gut. The subsequent course was studied using venograms and autopsy examination. In 10 of the animals Tromexan was administered before operation and continued postoperatively.

Twenty-seven dogs survived for over 10 days. Twenty-three showed x-ray and autopsy deligation and luminal reconstitution of the cava. In the series as a whole the use of absorbable gut resulted in a high percentage of later deligation and recanalization of the venous lumen. It was found that extensive distal venous thrombosis could be prevented by early postoperative use of Tromexan.

Saphenous venous pressure was high immediately after operation but it dropped and leveled off at an elevated point 1 hour later. With the reestablishment of the circulation through the inferior vena cava, the pressure gradually decreased.

ABRAMSON

Glover, R. P.: The Present Status of Patients Subjected to Mitral Commissurotomy Five or More Years Ago. Surg., Gynec. & Obst. **102:** 623 (May), 1956.

The author evaluated the effects of mitral commissurotomy on a series of 50 patients observed for 5 to 6½ years after operation. In 20 there was a definite history of rheumatic infection, while in every instance there was some degree of cardiorespiratory functional incapacity. Twenty-seven patients had experienced 1 or more bouts of congestive failure, 23 gave a history of gross hemoptysis, and 6 had had arterial emboli from which they recovered with some residual damage.

Three patients died within the first postoperative month. The cause of death was the production of too much valvular insufficiency in 2 and surgical shock in the third. An additional 6 patients had died within a 3-year period. Forty-one patients were living approximately 5 years or more after surgery.

The author pointed out that if one were to judge the present clinical status of patients with commissurotomy on the basis of their murmurs alone, it would be impossible to reach any definitive conclusion. However, he believes that, as assayed both subjectively and objectively, the operation has been of value to the majority of patients so treated. Furthermore, the degree of improvement obtained at the end of the first postoperative year has been maintained over a 5-year period.

ABRAMSON

Lewis, F. J., Varco, R. L., Taufic, M., and Niazi, S. A.: Direct Vision Repair of Triatrial Heart and Total Anomalous Pulmonary Venous Drainage. Surg., Gynec. & Obst. **102:** 713 (June), 1956.

The authors presented the results of surgical treatment, using hypothermia and direct vision repair, in 2 unusual congenital cardiac anomalies. In both cases there was an abnormal joining of the pulmonary veins and the atria. One was a triatrial heart, and the other, total anomalous pulmonary venous drainage with entry of all the pulmonary veins into the right atrium. In the latter instance, the only blood received by the left atrium was that which flowed through the patent foramen ovale.

In the patient with the triatrial heart the left atrium was divided by a septum into 2 chambers—a posterior-superior cavity into which all of the pulmonary veins entered, and an anterior-inferior cavity which led into the left ventricle through a normal mitral valve. The third atrial chamber was opened while a finger in the left atrium invaginated the abnormal septum into the third chamber, and then the septum was divided under direct vision.

In the patient with total anomalous pulmonary venous drainage, the right atrium was opened under direct vision, the atrial septal defect was enlarged and then the right atrium was reconstructed. The 4 pulmonary veins were directed through the atrial septal defect into the left atrium.

ABRAMSON

Foley, P. J., Allen, E. V., and James, J. M.: Surgical Treatment of Acquired Arteriovenous Fistulas. Am. J. Surg. **91:** 611 (April), 1956.

The authors studied 32 patients with traumatic arteriovenous fistulas who had been treated with quadruple ligation and excision of the lesion. Good follow-up data were available on 24 of these subjects. Of this number 4 had involvement of an upper limb and 20 of a lower limb. Of the latter, 10 had residual arterial insufficiency while the remainder demonstrated an adequate circulation. In all 4 patients with upper extremity lesions there was some impaired use of the involved arm. In most of the cases in the group, symptoms of venous insufficiency existed.

The authors concluded that, when possible, the surgeon should attempt to reestablish arterial and venous continuity in the lower limb when treating traumatic arteriovenous fistula. If this cannot be done, satisfactory results may be obtained in most instances with quadruple ligation and excision.

ABRAMSON

Hoagland, R. J.: Cardiac Involvement in Infectious Mononucleosis. Am. J. M. Sc. **232:** 252 (Sept.), 1956.

The previous literature on this subject is reviewed by the author, who finds the reported incidence of electrocardiographic abnormalities in infectious mononucleosis to vary from 5 to 50 per cent. The present study concerns the clinical and electrocardiographic findings in 100 consecutive hospital patients with mononucleosis. Electrocardiograms of 5 of the 100 patients revealed abnormalities. The changes consisted of prolongation of the P-R interval, complete atrioventricular heart block,

prolonged Q-T interval, and flattened T wave in lead II. The high incidence of electrocardiographic abnormalities reported elsewhere may be related to an incorrect diagnosis of mononucleosis or to interpretation of the electrocardiograms in which the so-called "changes" were within normal limits. In this report, mononucleosis was thought to be established on the basis of hematologic and serologic data. The findings indicate that myocarditis is not a clinically recognizable feature of mononucleosis.

SHUMAN

Cruz, P. T., and Stambaugh, E. F.: Intracardiac Extension of a Bronchogenic Carcinoma. Dis. of Chest **29:** 441 (April), 1956.

A rare case of bronchogenic carcinoma with invasion of the median pulmonary vein and a pedunculated extension into the left atrium and ventricle is presented. There were no other sites of metastases. The authors discuss the varied histology at different areas in the tumor mass with relation to our present histologic classification of bronchogenic carcinoma.

MAXWELL

Pansch, I.: Functional Mitral Stenosis due to Myxoma. Ztschr. Kreislaufforsch. **45:** 619 (Aug.), 1956.

Typical symptoms of mitral stenosis (including accentuation of the first heart sound) were present in a man who died in pulmonary edema and in whom an apple-sized myxoma of the left atrium was found at autopsy. The myxoma was attached to the posterior wall of the atrium while the mitral valves were completely normal. The patient had previously reported sudden episodes of unconsciousness during work.

LEPESCHKIN

VASCULAR DISEASE

Meltzer, J. I.: Pericardial Effusion in Generalized Scleroderma. Am. J. Med. **20:** 638 (April), 1956.

The author describes 2 patients with pericardial effusion apparently due to involvement of the pericardium in scleroderma. The pericarditis associated with scleroderma may have a protracted course and may not significantly contribute to disability over long periods of time. The fluid in both patients was similar, characterized by high protein, low cell count, absence of blood, and negative culture. In 1 patient the electrophoretic patterns of the heparinized pericardial fluid and of the plasma were virtually identical.

HARRIS

Zendel, J. F., and Paulin, C.: Prolonged Shock in Dissecting Aortic Aneurysm. Arch. Int. Med. **98:** 106 (July), 1956.

A case of prolonged shock associated with a dissecting aneurysm of the aorta is described. The shock responded to therapy with levarterenol (Levophed) until death resulted from rupture of the aneurysm into the pericardial sac, with resultant cardiac tamponade. P-wave changes described in atrial infarction were found in the electrocardiogram.

This case further demonstrates that the electrocardiographic findings may also be misleading. While there were no changes typical of myocardial infarction, the rapidly changing pattern would be consistent with this diagnosis. The P-wave changes seen in the first electrocardiogram, suggesting atrial infarction, may actually have been due to the diffuse subendocardial hemorrhage of the right atrium found after death. Electrolyte disturbances associated with azotemia, particularly hyperpotassemia, undoubtedly contributed to the changes seen in the last 2 electrocardiograms.

BERNSTEIN

Lofgren, K. A., Myers, T. T., and Webb, W. D., Jr.: Recurrent Varicose Veins. Surg., Gynec. & Obst. **102:** 729 (June), 1956.

The authors studied a group of 341 patients who underwent 510 surgical procedures for recurrent varicose veins. All previous operations had consisted of ligation followed by sclerosing therapy, except in 2 patients, who had undergone incomplete stripping procedures. In about 80 per cent of patients further surgery was performed within 10 years after the original ligation. Outstanding characteristics of recurrent varicose veins were: incompetency of superficial and perforator veins in thigh, leg, and foot, and inadequacy of ligation at the saphenofemoral or saphenopopliteal junctures.

The authors stress the importance of correctly diagnosing the presence and location of incompetent veins prior to operation, so that all of them can be adequately treated surgically, and of proper ligation of vessels at the saphenofemoral or saphenopopliteal junctures. They indicate that eradication of all incompetent veins is the most effective preventive measure against recurrence.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

APPLICATIONS FOR AHA RESEARCH SUPPORT NOW BEING INVITED

Applications by research investigators for support of projects to be developed during the fiscal year beginning July 1, 1958 are now being accepted by the Association.

The deadline for research fellowship applications and established investigatorships is September 15, 1957. Applications for grants-in-aid must be made by November 1, 1957.

Funds for Association-supported research in the cardiovascular field are provided by public contributions to the Heart Fund. At least half of all funds received by the American Heart Association's National Office are allocated to research. Approximately $20 million have been allocated for research support by the Association and its state and local affiliates or chapters in the past nine years.

Applications may be made for awards in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $8,000 yearly, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. Applicants for Established Investigatorships may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,800 to $5,700.

Advanced Research Fellowships are to be awarded for the first time next year for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not yet clearly qualified to conduct their own independent research. They will be permitted to spend up to 25 per cent of their time in professional and scientific activities not strictly of research nature, providing that these will contribute to their professional development and do not involve services for a fee. These new stipends range from $4,600 to $6,500 annually.

Grants-in-Aid: Made to experienced investigators to provide support for specified projects.

The Association also maintains another and unique form of research support, the Career Investigatorship. This is given to a limited number of scientific investigators of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career investigators are selected on the initiative of the Research Committee of the Association and not by application.

Further information and applications may be obtained from the Medical Director, American Heart Association, 44 East 23rd. Street, New York 10, N. Y. Research fellowship application forms are to be used in making application for the Advanced Research Fellowship award. Classification of the applicant as Research Fellow or Advanced Research Fellow is at the discretion of the American Heart Association's Research Committee.

MEMORIAL LECTURERS CHOSEN FOR SCIENTIFIC SESSIONS

The Memorial Lecturers who have been chosen for the 30th Scientific Sessions of the American Heart Association (Chicago, October 25–28), are: Charles W. Rammelkamp, Jr., M.D., Professor of Medicine, Western Reserve University, who will give the Lewis A. Conner Memorial Lecture on Saturday morning, October 26, and Nelson W. Barker, M.D., Professor of Medicine, Mayo Foundation, who will deliver the George E. Brown Memorial Lecture on Sunday morning.

Dr. Rammelkamp has made outstanding contributions in the field of streptococcal

control and prevention of rheumatic fever. Dr. Barker is one of the leading clinicians in the field of peripheral vascular disease and has published many papers on the subject.

The Association's Scientific Sessions, to be held at the Hotel Sherman, will commemorate the Tercentenary of William Harvey.

One of the innovations this year will be an all-day scientific program on Friday, October 26, for physicians in general practice. The morning session will be devoted to "Prevention and Management of Cardiovascular Emergencies." An afternoon panel will be held on the same subject, to be followed by a second panel on "Unsettled Questions in Relation to Management of Cardiovascular Disease." Among these questions are diet, rehabilitation and indications for referral to surgery.

A special Friday evening scientific program will be held on "Instrumental Methods in Cardiovascular Diagnosis."

The regular Scientific Sessions will get underway Saturday morning with a brief dedication ceremony honoring William Harvey. Scheduled for Saturday morning, in addition to the Conner Memorial Lecture, are presentation of the Albert Lasker Award of the American Heart Association and a General Session. The Council on Rheumatic Fever and Congenital Heart Disease will hold a luncheon on Saturday.

The Saturday afternoon program includes Special Sessions of the Sections on Clinical Cardiology and on Circulation, and of the Council on Rheumatic Fever and Congenital Heart Disease.

A General Session is scheduled for Sunday morning, and will include the Brown Memorial Lecture. The Community Service and Education Council will hold a luncheon on Sunday, which includes an address and the election of the Council's officers. The Council has also scheduled a Sunday afternoon session, jointly with the Staff Conference of Heart Associations, on "Community Service—Its Significance for Heart Associations." This program is of interest to all physicians who have responsibilities for community service programs conducted by Heart Associations.

In addition, the Community Service and Education Council will sponsor a Sunday afternoon scientific panel, to be organized by Dr. Herbert Pollack, on "The Present Status of Fat Metabolism and Atherosclerosis."

The Association's Annual Dinner, including the presentation of awards, will be held Sunday evening.

Special Sessions of the Sections on Basic Science and on Cardiovascular Surgery and the Council for High Blood Pressure Research will conclude the Scientific Sessions on Monday morning.

Six Assembly Panels will be in sesssion on Monday. The Panels will deal with Research; Fund Raising and Public Relations; Relationships and Responsibilities between national, state and local Heart Associations; Community Service; Heart Association Support of Medical Schools; and Heart Association Services to Professional Groups. Recommendations made by these six Panels will be reviewed by the full Assembly on Tuesday morning, at which time officers of the Association and Board members will be elected.

MICHAEL REESE HOSPITAL, CHICAGO, OFFERS ECG COURSE

A course in Electrocardiographic Interpretation for graduate physicians will be given at the Michael Reese Hospital, Chicago, by Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, and his associates. Classes will meet daily from 9:00 A.M. to 5:00 P.M., August 19 through August 31.

Further information and a lecture schedule may be obtained by writing to Mrs. Margaret Stern, Administrative Assistant, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

MEETINGS CALENDAR

June 16–21: American Society for Pediatric Research, Carmel, Calif. Sydney S. Gellis, 330 Brookline Ave., Boston 15, Mass.

June 17–19: American Pediatric Society, Carmel, Calif. A. C. McGuinness, 1427 Eye Street, N.W., Washington 5, D. C.

September 9–12: U.S. Section, International College of Surgeons, Chicago, Ill. Karl Meyer, 1516 Lake Shore Dr., Chicago, Ill.

September 29–October 4: College of American Pathologists, New Orleans, La. A. H. Dearing, Prudential Plaza Suite 2115, Chicago 1, Ill.

October 1–4: American Roentgen Ray Society, Washington, D. C. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

October 7–10: American Academy of Pediatrics, Chicago, Ill. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.

October 14–18: American College of Surgeons, Atlantic City, N. J. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

October 14–19: American Society of Anesthesiologists, Los Angeles, Calif. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 21–23: Association of American Medical Colleges, Atlantic City, N. J. Dean F. Smiley, 2530 Ridge Ave., Evanston, Ill.

October 23–25: American Association of Medical Clinics, Kansas City, Mo. Harold D. Caylor, Caylor-Nickel Clinic, Bluffton, Ind.

October 25–28: Scientific Sessions of the American Heart Association, Chicago, Ill. American Heart Association, 44 East 23rd St., New York 10, N. Y.

October 28–30: Association of Military Surgeons of U. S., Washington, D. C. R. E. Bitner, 1726 I St., N.W., Washington 6, D. C.

November 3–4: American Society for the Study of Arteriosclerosis, Chicago, Ill. O. J. Pollak, M.D., P.O. Box #228, Dover, Del.

November 11–15: American Public Health Association, Cleveland, Ohio. R. M. Atwater, 1790 Broadway, New York 19, N. Y.

November 17–22: Radiological Society of North America, Chicago, Ill. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y.

ABROAD

June 3–7: Harvey Tercentenary Congress, London. D. Geraint James, M.D., M.R.C.P., 11 Chandos St., Cavendish Square, London W.1.

June 23–28: International Congress on Rheumatic Diseases, Toronto, Ont. International Congress on Rheumatic Diseases, P.O. Box 237, Terminal "A", Toronto, Ontario, Canada.

July 7–13: Brazilian Congress of Cardiology and Angiology, Rio de Janeiro. Dr. A. de Carvalho Azevedo, Rua Domingos Ferreira 28, Rio de Janeiro, Brazil.

July 14–19: International Gerontological Congress, Merano-Bolzano, Italy. Segreteria, Quarto Congresso Internazionale de Gerontologia, Viale Morgagni 85, Firenze, Italy.

July 21–28: International Congress of Neurological Sciences, Brussels, Belgium. Pearce Bailey, M.D., National Institutes of Health, Bethesda 14, Md.

July 24–29: International Congress of Nutrition, Paris. Congress International de Nutrition, 71 Blvd. Pereire, Paris 17e, France.,

September 29–October 5: World Medical Association, Istanbul, Turkey. Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y.

October 27–November 2: Congress of International Society of Surgery, Mexico City, Mexico. Dr. L. Dejardin, 141 rue Belliard, Brussels, Belgium.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

CONTRIBUTORS TO THIS ISSUE

WALTER H. ABELMANN, M.D.

Associate in Medicine, Harvard Medical School; Assisting Physician, Boston City Hospital; Assistant Physician, Thorndike Memorial Laboratory, Boston, Mass. Established Investigator, American Heart Association.

J. B. ARMSTRONG, M.D., F.R.C.P. (Canada)

Assistant Professor, Department of Physiology and Medical Research of the University of Manitoba; Assistant Physician, Winnipeg General Hospital, Winnipeg, Canada; Markle Scholar in Medical Science.

N. S. ASSALI, M.D.

Associate Professor of Obstetrics and Gynecology, University of California at Los Angeles, Calif.

SAUL P. BAKER, M.Sc., M.D.

Senior Assistant Resident Physician, Department of Medicine, the University of Chicago, Chicago, Ill.; Formerly, Senior Assistant Surgeon (R), Gerontology Branch, National Heart Institute, National Institutes of Health, U. S. Public Health Service, Bethesda and the Baltimore City Hospitals, Baltimore, Md.; Assistant Visiting Physician, Department of Medicine, Baltimore City Hospitals, Baltimore, Md.

OSCAR J. BALCHUM, M.D., PH.D.

Research Fellow of the American Heart Association, Department of Medicine, University of Colorado School of Medicine, Denver, Colo.

SAMUEL BELLET, M.D.

Director, Division of Cardiology, Philadelphia General Hospital; Director, Division of Cardiovascular Disease, Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa.

S. GILBERT BLOUNT, JR., M.D.

Associate Professor of Medicine; Director, Cardiovascular Laboratory, University of Colorado School of Medicine, Denver, Colo.

DANIEL A. BRODY, M.D.

Associate Professor, Department of Medicine, University of Tennessee, Memphis, Tenn.

R. M. CHERNIACK, M.D., M.Sc., F.R.C.P. (Canada)

Assistant Professor, Department of Physiology and Medical Research of the University of Manitoba; Assistant Physician, Winnipeg General Hospital, Winnipeg, Canada; Consultant in Respiratory Diseases, D.V.A. Deer Lodge Hospital; Markle Scholar in Medical Science.

JAMES CONWAY, M.D., Ph.D.

Senior Lecturer in Physiology in the University of London; Clinical Assistant to the Cardiac Department, Charing Cross Hospital Medical School, London, England.

T. E. CUDDY, M.D.

Resident in Medicine, Winnipeg General Hospital. Winnipeg, Canada.

GEORGE W. DEITZ III, M.D.

Assistant, Division of Cardiology, Philadelphia General Hospital; Assistant Physician, Germantown Hospital, Philadelphia; Instructor in Cardiology, Graduate School of Medicine, University of Pennsylvania; Medical Consultant, Friends Hospital, Philadelphia, Pa.

FREDERIC ELDRIDGE, M.D.

Assistant Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.

LAURENCE B. ELLIS, M.D.

Associate Clinical Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Memorial Laboratory; Visiting Physician, Director, Electrocardiographic Laboratory and Chief, Cardiac Clinic, Boston City Hospital, Boston, Mass.

E. HARVEY ESTES, JR., M.D.

Associate in Medicine, Department of Medicine, Duke University, Durham, N. C.

EVAN FLETCHER, M.D.

Consultant Physician, Internal Medicine Mid Ulster Hospital, Belfast City Hospital, Musgrave Park Hospital, Ministry of Pensions and Ulster Volunteer Force Hospital, Ministry of Labor, Government of Northern Ireland; Hon. Assistant Biochemical Research Laboratory, Queens University, Belfast, Ireland.

THOMAS B. GIBBONS, M.D., M.S.

Formerly, Senior Associate, Department of Medicine, The Mason Clinic; Clinical Assistant in Medicine, University of Washington, Seattle, Wash.; Presently, Albuquerque, N. M.

MICHAEL A. GRAVALLESE, JR., M.D.

Clinical Instructor in Medicine at University of California Medical School, San Francisco Hospital, San Francisco, Calif.

DWIGHT E. HARKEN, M.D.

Associate Clinical Professor of Surgery, Harvard Medical School, Boston, Mass.; Thoracic Surgeon, Peter Bent Brigham Hospital, Mount Auburn Hostal, and Malden Hospital.

D. Mark Hegsted, Ph.D.

Associate Professor of Nutrition, Harvard School of Public Health, Boston, Mass.

Herbert Hultgren, M.D.

Associate Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.

Franklin D. Johnston, M.D.

Professor of Internal Medicine, University of Michigan Medical School; Heart Station, University Hospital, Ann Arbor, Mich.

Robert L. King, M.D., F.A.C.P.

Chief, Department of Medicine, The Mason Clinic; Clinical Associate Professor of Medicine, University of Washington, Seattle, Wash.

James J. Leonard, M.D.

Trainee in Cardiology, National Heart Institute, United States Public Health Service, Instructor in Medicine, Duke University, Durham, N. C.

Jack Margolis, M.D.

Chief of the Medical Service, Veterans Administration Hospital, Big Spring, Tex.

Henry J. L. Marriott, M.D.

Associate Professor of Medicine, University of Maryland School of Medicine; Chief, Electrocardiograph Department, Mercy Hospital, Baltimore, Md.

Henry D. McIntosh, M.D.

Associate in Medicine, Department of Medicine, Duke University, Durham, N. C.

W. R. Meadows, M.D.

Assistant Chief of Medicine, Veterans Administration Hospital, Palo Alto, Calif.

Ralph F. Morton, M.D.

Instructor and Frank W. Dugan Fellow in Cardiology, Department of Medicine, University of Tennessee, Memphis, Tenn.

Simon Rodbard, M.D., Ph.D.

Professor of Experimental Medicine and Director of the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y.

J. Roller, M.D.

Research Assistant, Department of Obstetrics and Gynecology, University of California at Los Angeles, Calif.

William E. Romans, B.S.

Formerly, Research Assistant, University of Tennessee, Presently, Southwestern Medical Division, University of Texas, Dallas, Tex.

Nevin S. Scrimshaw, Ph.D., M.D.

Director, Institute of Nutrition, Central America and Panama, Guatemala City; Visiting Lecturer, Harvard School of Public Health, Boston, Mass.

Arthur Selzer, M.D.

Associate Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.

K. Shirley Smith, M.D., F.R.C.P.

Consultant Physician, in charge of the Cardiac Department, Charing Cross Hospital, London, England.

Fredrick J. Stare, M.D.

Professor of Nutrition and Chairman of the Department of Nutrition, Harvard School of Public Health, Boston, Mass.

Henry Swan, M.D.

Professor and Head, Department of Surgery, University of Colorado School of Medicine, Denver, Colo.

Carlos Tejada, M.D.

Chief of Pathology, Institute of Nutrition, Central America and Panama, Guatemala City, Central America.

Martha F. Trulson, D.Sc.

Assistant Professor of Nutrition, Harvard School of Public Health, Boston, Mass.

Jack Van Elk, M.D.

Research Fellow of the Colorado Heart Association, Department of Medicine, University of Colorado School of Medicine, Denver, Colo.

Maurice Victor, M.D.

Assistant Neurologist, Massachusetts General Hospital, Clinical Associate in Neurology, Harvard Medical School, Boston, Mass.

J. Voskian, M.D.

Research Assistant, Department of Obstetrics and Gynecology, University of California at Los Angeles, Calif.

James V. Warren, M.D.

Professor of Medicine, Department of Medicine, Duke University, Durham, N. C.

Arnold M. Weissler, M.D.

American Heart Association Research Fellow, Instructor in Medicine, Department of Medicine, Duke University, Durham, N. C.

Paul D. White, M.D.

President, International Society of Cardiology. Consultant in Medicine, Massachusetts General Hospital; Clinical Professor of Medicine, Emeritus, Harvard University.

CIRCULATION

Official Journal of the American Heart Association

VOLUME XV
January–June, 1957

GRUNE & STRATTON, INC.
NEW YORK AND LONDON

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

EDITOR-IN-CHIEF

HERRMAN L. BLUMGART, *Boston, Mass.*

EDITH E. PARRIS, *Assistant Editor*

EDITORIAL BOARD

BENJAMIN M. BAKER, *Baltimore, Md.*
JANET S. BALDWIN, *New York, N. Y.*
SAMUEL BELLET, *Philadelphia, Pa.*
RICHARD J. BING, *St. Louis, Mo.*
J. SCOTT BUTTERWORTH, *New York, N. Y.*
W. EDWARD CHAMBERLAIN, *Philadelphia, Pa.*
A. C. CORCORAN, *Cleveland, Ohio*
ANDRÉ COURNAND, *New York, N. Y.*
JEFFERSON M. CRISMON, *Stanford, Calif.*
THADDEUS S. DANOWSKI, *Pittsburgh, Pa.*
CLARENCE DE LA CHAPELLE, *New York, N. Y.*
CHARLES T. DOTTER, *Portland, Ore.*
JESSE E. EDWARDS, *Rochester, Minn.*
A. STONE FREEDBERG, *Boston, Mass.*
CHARLES K. FRIEDBERG, *New York, N. Y.*
HARRY GOLDBLATT, *Cleveland, Ohio*
ROBERT E. GROSS, *Boston, Mass.*
DWIGHT E. HARKEN, *Boston, Mass.*
EDGAR A. HINES, JR., *Rochester, Minn.*
FRANKLIN D. JOHNSTON, *Ann Arbor, Mich.*
AARON KELLNER, *New York, N. Y.*
H. M. MARVIN, *New Haven, Conn.*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*
DAVID F. OPDYKE, *Rahway, N. J.*
GEORGE A. PERERA, *New York, N. Y.*
DICKINSON W. RICHARDS, *New York, N. Y.*
DAVID D. RUTSTEIN, *Boston, Mass.*
HOWARD B. SPRAGUE, *Boston, Mass.*
ISAAC STARR, *Philadelphia, Pa.*
HELEN B. TAUSSIG, *Baltimore, Md.*
GEORGE E. WAKERLIN, *Chicago, Ill.*
JAMES V. WARREN, *Durham, N. C.*
JAMES WATT, *Bethesda, Md.*
CHARLES C. WOLFERTH, *Philadelphia, Pa.*
IRVING S. WRIGHT, *New York, N. Y.*

ASSOCIATE EDITORS

EDGAR V. ALLEN, *Rochester, Minn.*
STANFORD WESSLER, *Boston, Mass.*
PAUL M. ZOLL, *Boston, Mass.*

PUBLICATIONS COMMITTEE OF THE SCIENTIFIC COUNCIL
AMERICAN HEART ASSOCIATION

IRVING S. WRIGHT, *Chairman*
New York, N. Y.

PAUL S. BARKER, *Ann Arbor, Mich.*
STANLEY E. BRADLEY, *New York, N. Y.*
J. SCOTT BUTTERWORTH, *New York, N. Y.*
IRVING B. HEXTER, *Cleveland, Ohio*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*
GEORGE E. WAKERLIN, *Chicago, Ill.*

EUGENE B. FERRIS, *Medical Director, American Heart Association, New York, N. Y.*

HERRMAN L. BLUMGART, *Boston, Mass.*
HOWARD P. LEWIS, *Portland, Ore.*
CARL J. WIGGERS, *Cleveland, Ohio*

Interlingua Summaries by Science Service, Division de Interlingua, New York, N.Y., ALEXANDER GODE, Chief.

VOLUME XV

January–June, 1957

22-A

CIRCULATION

Official Journal of the American Heart Association

No. 1

EDITORIAL

PATHOGENESIS OF ESSENTIAL HYPERTENSION ..... *George E. Wakerlin* 1

PRESENT STATUS OF DIAGNOSIS AND TREATMENT OF PHEOCHROMOCYTOMA
U. S. von Euler and G. Ström 5

EFFECT OF CARDIAC CONTRACTION ON CORONARY BLOOD FLOW
David C. Sabiston and Donald E. Gregg 14

ARTERIAL HOMOGRAFTS FOR PERIPHERAL ARTERIOSCLEROTIC OCCLUSIVE DISEASE
Michael E. De Bakey, E. Stanley Crawford, Oscar Creech and Denton A. Cooley 21

DIFFERENTIAL EFFECT OF DIETARY FAT AND WEIGHT REDUCTION ON SERUM LEVELS OF BETA-LIPOPROTEINS
Weldon J. Walker, Norman Weiner and Lawrence J. Milch 31

PRIMARY PULMONARY HYPERTENSION: REVIEW OF LITERATURE AND RESULTS OF CARDIAC CATHETERIZATION IN TEN PATIENTS
Don W. Chapman, Jack P. Abbott and Joseph Latson 35

COMPARISON IN MAN OF ADRENERGIC BLOCKADE PRODUCED BY DIBENZYLINE, ILIDAR, PRISCOLINE, AND REGITINE ..... *Harold D. Green* 47

A HEART FUNCTION TEST WITH CONTINUOUS REGISTRATION OF OXYGEN CONSUMPTION AND CARBON DIOXIDE PRODUCTION
J. Jongbloed, C. L. C. Van Nieuwenhuizen and H. Van Goor 54

ALVEOLAR WALLS IN MITRAL STENOSIS
Robert M. O'Neal, Wilbur A. Thomas, Kyu Taik Lee and Erwin R. Rabin 64

SYMPOSIUM ON THE U WAVE OF THE ELECTROCARDIOGRAM

INTRODUCTION ..... *Eugene Lepeschkin* 68

II. VARIOUS TYPES OF FUSION BETWEEN T AND U WAVES
Max Holzmann 70

VI. GENESIS OF THE U WAVE ..... *Eugene Lepeschkin* 77

XI. COUPLING INTERVALS OF VENTRICULAR EXTRASYSTOLES IN RELATION TO THE HEART RATE, THE U WAVE AND THE SUPERNORMAL PHASE OF EXCITABILITY ..... *Eugene Lepeschkin and Mauricio B. Rosenbaum* 82

XII. POLARITY AND AMPLITUDE OF THE U WAVE OF THE ELECTROCARDIOGRAM IN RELATION TO THAT OF THE T WAVE
Borys Surawicz, Robert L. Kemp and Samuel Bellet 90

XIII. PROGNOSTIC SIGNIFICANCE OF NEGATIVE U WAVES IN THE ELECTROCARDIOGRAM IN HYPERTENSION
Robert L. Kemp, Borys Surawicz, John C. Bettinger, Harry Gottlieb and Samuel Bellet 98

XIV. CLINICAL STUDY OF THE ABNORMALITIES OF THE TERMINAL COMPLEX TU-U OF THE ELECTROCARDIOGRAM ..... *Joseph Lambert* 102

XV. U WAVE IN CORONARY DISEASE ..... *Cornelio Papp* 105

Clinical Conference

Symposium on Coronary Dilatory Drugs

Lloyd L. Hefner, Ben Friedman, T. Joseph Reeves, E. E. Eddleman, Jr. and Tinsley R. Harrison 111

Clinical Progress

Procaine Amide: A Review

Herbert J. Kayden, B. B. Brodie and J. Murray Steele 118

Books Received ... 127

Book Reviews ... 129

Abstracts ... 133

American Heart Association ... 150

Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections

Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, Charles H. Rammelkamp, Chairman 154

Contributors to this Issue ... 159

No. 2

Editorial

Constrictive Pericarditis ... *C. Sidney Burwell* 161

The Lewis A. Conner Memorial Lecture: Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease

Jesse E. Edwards 164

Clinical and Anatomic Features in Five Hundred Patients with Fatal Acute Myocardial Infarction

Kyu Taik Lee, Wilbur A. Thomas, Erwin R. Rabin and R. M. O'Neal 197

Relation of the Postcommissurotomy Syndrome to the Rheumatic State

Daniel L. Larson 203

Ebstein's Anomaly ... *S. Gilbert Blount, Jr., Malcolm C. McCord and Ira J. Gelb* 210

Effect of Prolonged Steroid Therapy for Rheumatic Fever on the Exchangeable Potassium Content and Body Weight ... *Jerry K. Aikawa* 225

Pressor Effects of Norepinephrine After Drastic Reduction of Sodium Intake ... *L. K. Dahl* 231

Thrombotic Obliteration of the Branches of the Aortic Arch

Robert B. Kalmansohn and Richard W. Kalmansohn 237

Measurement of Cardiac Output and Central Volume by a Modified Decholin Test of Circulation Time

Hadley L. Conn, Jr., Donald F. Heiman and Claude R. Joyner 245

Effect of Cigarette Smoking on Coronary Blood Flow and Myocardial Metabolism ... *L. M. Bargeron, Jr., D. Ehmke, F. Gonlubol, A. Castellanos, A. Siegel and R. J. Bing* 251

Chest Pain in Patients with Isolated Pulmonic Stenosis

Richard P. Lasser and Gabriel Genkins 258

Immunologic Evidence of Group A Streptococcal Infection in Patients Undergoing Mitral Commissurotomy ... *Gene H. Stollerman, William F. Lynch, Mario A. Dolan, Dennison Young and John B. Schwedel* 267

Effects of Meals of Different Fats on Blood Coagulation

Ancel Keys, Ratko Buzina, Francisco Grande and Joseph T. Anderson 274

Experimental Responses of the Human Body to a Known Periodic Force as a Measure of Ballistocardiographic Fidelity
G. P. Wilson, D. M. Cunningham and H. E. Griswold, Jr. 280
Clinical Progress
The Artificial Kidney—Past, Present, and Future ..... *W. J. Kolff* 285
Abstracts 295
American Heart Association 316
Contributors to this Issue 319

No. 3

Editorial
Gallop Rhythm ..... *James V. Warren* 321
Variations in Serum Glutamic Oxaloacetic Transaminase Activity in Experimental and Clinical Coronary Insufficiency, Pericarditis, and Pulmonary Infarction
Irwin Nydick, Paul Ruegsegger, Felix Wróblewski and John S. LaDue 324
Ventricular Dynamics in Atrial Fibrillation
Harold T. Dodge, Frederic T. Kirkham, Jr., and Clara V. King 335
Distribution of Pain in Myocardial Infarction ..... *Kenneth Kreines* 348
Relationship of Platelet Serotonin to Disturbances of Clotting and Hemostasis ..... *Murray Weiner and Sidney Udenfriend* 353
Isolated Congenital Mitral Stenosis: Report of Two Cases with Mitral Valvotomy in One ..... *J. L. Braudo, S. N. Javett, D. I. Adler and I. Kessel* 358
Biochemical Observations of Human Atheromatosis: Analysis of Aortic Intima ..... *Nancy L. Noble, Robert J. Boucek and Kung-Ying Tang Kao* 366
Cardiovascular Disturbances in Chronic Severe Anemia
L. M. Sanghvi, R. Sharma and S. N. Misra 373
Effect of Morphine and N-Allylnormorphine on Cerebral Hemodynamics and Oxygen Metabolism
John H. Moyer, Robert Pontius, George Morris and Robert Hershberger 379
Primary Mesothelioma of the Pericardium
John Thomas and James M. Phythyon 385
Failure of α-Phenylbutyrate and β-Phenylvalerate in Treatment of Hypercholesterolemia ..... *Donald S. Fredrickson and Daniel Steinberg* 391
Congenital Absence of the Pulmonary Valve
Lucien A. Campeau, Paul E. Ruble and Warren B. Cooksey 397
Assay of Anti-Anginal Agents: I. A Curve Analysis with Multiple Control Periods ..... *Seymour L. Cole, Harry Kaye and George C. Griffith* 405
Hemodynamic Alterations in Hemorrhagic Fever
George Entwisle and Edward Hale 414
Clinical Evaluation of a New Oral Nonmercurial Diuretic
Benjamin Wainfeld, Jacob J. Yarvis and Arthur Fankhauser 426
Relationship of Left Atrial Volume to Pulmonary Artery and Wedge Pressures in Mitral Stenosis
Louis A. Soloff, Jacob Zatuchni and George E. Mark, Jr. 430
Extreme Bilateral Atriomegaly: Review of the Literature and Report of a Case ..... *Wayne R. Rogers and Benjamin Wittels* 434
Clinical Conference
Myxedema Heart Disease ..... *John D. Hamilton and W. F. Greenwood* 442

Clinical Progress

Velocity of Blood Flow in Health and Disease
Leslie E. Morris and Herrman L. Blumgart 448

Abstracts ... 461

American Heart Association ... 476

Contributors to this Issue ... 479

No. 4

Editorial

Auditory and Visual Perception of Cardiac Vibrations
J. Scott Butterworth 481

Aortic Aneurysm: Report of 101 Cases
Brooke Roberts, Gordon Danielson and William S. Blakemore 483

Pulmonary Function in Left Ventricular Failure, Including Cardiac Asthma
Richard S. Cosby, Ellery Cory Stowell, Jr., W. Ray Hartwig and Mary Mayo 492

Diagnostic and Prognostic Significance of Serum Transaminase Levels in Coronary Occlusive Disease ... *A. A. Kattus, R. Watanabe and C. Semenson* 502

Cardiovascular Function in Hypothermic Anesthetized Man
John C. Rose, Thomas F. McDermott, Lawrence S. Lilienfield, Frank A. Porfido and Robert T. Kelley 512

Vasomotor Responses in the Extremities of Subjects with Various Neurologic Lesions: I. Reflex Response to Warming
Walter Redisch, Francisco F. angco, Lothar Wertheimer, Arthur J. Lewis and J. Murray Steele 518

Bacterial Endocarditis Following Cardiac Surgery ... *Clarence Denton, Elias G. Pappas, Joseph F. Uricchio, Harry Goldberg and William Likoff* 525

"Left Heart" Radiopotassium Dilution Curves in Patients with Rheumatic Mitral Valvular Disease ... *Hadley L. Conn, Jr., Donald F. Heiman, William S. Blakemore, Peter T. Kuo and Stephen B. Langfeld* 532

Healed Dissecting Aneurysm in Cystic Medial Necrosis of the Aorta
Peter B. Hukill 540

Ventricular Arrhythmias after Intravenous Sodium Lactate in Heart Block ... *John F. Murray and S. H. Boyer* 547

Electrocardiographic and Plasma Potassium Responses Elicited on Cooling the Chest Wall of Man ... *Benjamin Kaminer and Ralph E. Bernstein* 559

Interatrial-Pressure Relationships after Closure of Atrial Septal Defects in Man ... *Albert H. Pemberton, John W. Kirklin and Earl H. Wood* 568

High Anterior Myocardial Infarction: XX. Studies on the Mechanism of Ventricular Activity
Myron Prinzmetal, Rexford Kennamer and Rashid A. Massumi 575

Indications and Contraindications for the Use of Molar Sodium Lactate
Samuel Bellet and Fred Wasserman 591

Clinical Progress

Digitalis and the Electrocardiogram ... *Alfred Pick* 603

Abstracts ... 609

American Heart Association ... 624

Congenital Cardiac Defects: A Physician's Guide for Evaluation and Management
Ruth Whittemore, S. Gilbert Blount, Jr., Sidney Blumenthal, Frank Glenn, Edward C. Lambert and Helen B. Taussig 631

Contributors to this Issue ... 639

No. 5

EDITORIAL

STAPHYLOCOCCI, ANTIBIOTICS AND ENDOCARDITIS ..... *Maxwell Finland* 641

GEORGE E. BROWN MEMORIAL LECTURE: OXYGEN TENSION OF TISSUES IN VIVO *Hugh Montgomery* 646

SURGICAL TREATMENT OF MITRAL INSUFFICIENCY BY TOTAL CIRCUMFERENTIAL "PURSE-STRING" SUTURE OF THE MITRAL RING *Robert P. Glover and Julio C. Davila* 661

SELECTIVE ROENTGENOGRAPHIC CONTRAST EXAMINATION AND ELECTROKYMOGRAPHY OF THE LEFT HEART IN EXPERIMENTAL MITRAL INSUFFICIENCY *Björn Nordenström, J P. Stamer, Jr., Melvin Figley and Herbert Sloan* 682

TREATMENT OF GANGRENE OF THE FEET AND LEGS BY WALKING ... *William T. Foley* 689

COR TRILOCULARE BIATRIATUM ..... *Donald Heath* 701

CLINICAL EVALUATION OF A NEW ORAL ANTICOAGULANT "SINTROM" *Emmett C. Neill, Richard Y. Moon and Joseph B. Vander Veer* 713

EFFECT OF CIRCULATORY CHANGES ON THE PULMONARY COMPLIANCE OF NORMAL SUBJECTS AND PATIENTS WITH MITRAL STENOSIS *W. W. Pryor, J. B. Hickam, H. O. Sieker and E. B. Page* 721

SPECIAL ARTICLE

KNOWLEDGE OF THE CIRCULATION BEFORE WILLIAM HARVEY *Arnold M. Katz* 726

CLINICAL PROGRESS

CARDIOVASCULAR DISTURBANCES IN POLIOMYELITIS ..... *Louis Weinstein* 735

CLINICAL CONFERENCE

CHRONIC PULMONARY EMPHYSEMA AND COR PULMONALE: A CLINICAL-PATHOLOGIC CONFERENCE *C. Bruce Taylor, Oglesby Paul, Armin F. Schick and George M. Hass* 757

BOOK REVIEWS 770

ABSTRACTS 775

AMERICAN HEART ASSOCIATION 795

CONTRIBUTORS TO THIS ISSUE 799

No. 6

EDITORIAL

REFLECTIONS ON ELECTROCARDIOGRAPHY ..... *Franklin D. Johnston* 801

SERUM LIPROPROTEIN AND CHOLESTEROL CONCENTRATIONS: COMPARISON OF RURAL COSTA RICAN, GUATEMALAN AND U. S. POPULATIONS *Nevin S. Scrimshaw, Martha Trulson, Carlos Tejada, D. Mark Hegsted and Fredrick J. Stare* 805

VALVULAR PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM: PHYSIOLOGIC CLINICAL RESPONSE TO OPEN VALVULOPLASTY *S. Gilbert Blount, Jr., Jack van Elk, Oscar J. Balchum and Henry Swan* 814

AGING OF ARTERIES IN RELATION TO HYPERTENSION *James Conway and K. Shirley Smith* 827

CIRCULATORY STUDIES IN WERNICKE'S ENCEPHALOPATHY: WITH SPECIAL REFERENCE TO THE OCCURRENCE OF A STATE OF HIGH CARDIAC OUTPUT AND POSTURAL HYPOTENSION ..... *Michael A. Gravallese, Jr. and Maurice Victor* 836

OBLITERATIVE BRACHIOCEPHALIC ARTERITIS: PULSELESS DISEASE OF TAKAYASU *Thomas B. Gibbons and Robert L. King* 845

THE AUSCULTATORY GAP IN ARTERIOSCLEROTIC HEART DISEASE *Simon Rodbard and Jack Margolis* 850

Comparison of Mercurial Diuretics and Bed Rest in Normal and Toxemic Pregnancies ..... *N. S. Assali, J. Voskian and J. Roller* 855
Significance of Pulmonary Elastic and Viscous Resistance in Orthopnea *R. M. Cherniack, T. E. Cuddy and J. B. Armstrong* 859
Stenosis of a Branch of the Pulmonary Artery: An Additional Cause of Continuous Murmurs over the Chest *Frederic Eldridge, Arthur Selzer and Herbert Hultgren* 865
Vasodepressor Syncope: Factors Influencing Cardiac Output *A. M. Weissler, J. V. Warren, E. H. Estes, Jr., H. D. McIntosh and J. J. Leonard* 875
Atrial Dissociation and Uniatrial Fibrillation *George W. Deitz III, Henry J. L. Marriott, Evan Fletcher and Samuel Bellet* 883
Heparin-Activated Clearing Factor: Standardized Test, Agewise Application, and Clinical Observations ..... *Saul P. Baker* 889
Cancellation of Esophageal Electrocardiograms *Ralph F. Morton, William E. Romans and Daniel A. Brody* 897
Idiopathic Myocardial Failure in the Last Trimester of Pregnancy and the Puerperium ..... *W. R. Meadows* 903
Special Article
The Evolution of our Knowledge about the Heart and its Diseases since 1628 ..... *Paul D. White* 915
Clinical Progress
Selection of Patients for Mitral and Aortic Valvuloplasty *Laurence B. Ellis, Walter H. Abelmann and Dwight E. Harken* 924
Abstracts 936
American Heart Association 955
Contributors to This Issue 959

INDEX OF AUTHORS

Abbott, J. P., 35
Abelmann, W. H., 924
Adler, D. I., 358
Aikawa, J. K., 225
Anderson, J. T., 274
Armstrong, J. B., 859
Assali, N. S., 855

Baker, S. P., 889
Balchum, O. J., 814
Bargeron, L. M., Jr., 251
Bellet, S., 90, 98, 591, 883
Bernstein, R. E., 559
Bettinger, J. C., 98
Bing, R. J., 251
Blakemore, W. S., 483, 532
Blount, S. G., Jr., 210, 631, 814
Blumenthal, S., 631
Blumgart, H. L., 448
Boucek, R. J., 366
Boyer, S. H., 547
Braudo, J. L., 358
Brodie, B. B., 118
Brody, D. A., 897
Burwell, C. S., 161
Butterworth, J. S., 481
Buzina, R., 274

Campeau, L. A., 397
Castellanos, A., 251
Chapman, D. W., 35
Cherniack, R. M., 859
Cole, S. L., 405
Conn, H. L., Jr., 245, 532
Conway, J., 827
Cooksey, W. B., 397
Cooley, D. A., 21
Cosby, R. S., 492
Crawford, E. S., 21
Creech, O., Jr., 21
Cuddy, T. E., 859
Cunningham, D. M., 280

Dahl, L. K., 231
Danielson, G., 483
Davila, J. C., 661
De Bakey, M. E., 21
Deitz, G. W., III, 883
Denton, C., 525
Dodge, H. T., 335
Dolan, M. A., 267

Eddleman, E. E., Jr., 111
Edwards, J. E., 164
Ehmke, D., 251
Eldridge, F., 865
Ellis, L. B., 924
Entwisle, G., 414
Estes, E. H., Jr., 875

Fankhauser, A., 426
Figley, M., 682
Finland, M., 641
Fletcher, E., 883
Foley, W. T., 689
Fredrickson, D. S., 391
Friedman, B., 111

Gelb, I. J., 210
Genkins, G., 258
Gibbons, T. B., 845
Glenn, F., 631
Glover, R. P., 661
Goldberg, H., 525
Gonlubol, F., 251
Gottlieb, H., 98
Grande, F., 274
Gravallese, M. A., Jr., 836
Green, H. D., 47
Greenwood, W. F., 442
Gregg, D. E., 14
Griffith, G. C., 405
Griswold, H. E., 280

Hale, E., 414
Hamilton, J. D., 442
Harken, D. E., 924
Harrison, T. R., 111
Hartwig, W. R., 492
Hass, G. M., 757
Heath, D., 701
Hefner, L. L., 111
Hegsted, D. M., 805
Heiman, D. F., 245, 532
Hershberger, R., 379
Hickam, J. B., 721
Holzmann, M., 70
Hukill, P. B., 540
Hultgren, H., 865

Javett, S. N., 358
Johnston, F. D., 801
Jongbloed, J., 54
Joyner, C. R., 245

Kalmansohn, R. B., 237
Kalmansohn, R. W., 237
Kaminer, B., 559
Kao, K.-Y. T., 366
Kattus, A. A., 502
Katz, A. M., 726
Kayden, H. J., 118
Kaye, H., 405
Kelley, R. T., 512
Kemp, R. L., 90, 98
Kennamer, R., 575
Kessel, I., 358
Keys, A., 274
King, C. V., 335
King, R. L., 845
Kirkham, F. T., Jr., 335
Kirklin, J. W., 568
Kolff, W. J., 285
Kreines, K., 348
Kuo, P. T., 532

LaDue, J. S., 324
Lambert, E. C., 631
Lambert, J., 102
Langfeld, S. B., 532
Larson, D. L., 203
Lasser, R. P., 258
Latson, J., 35
Lee, K. T., 64, 197
Leonard, J. J., 875
Lepeschkin, E., 68, 77, 82
Lewis, A. J., 518
Likoff, W., 525
Lilienfield, L. S., 512
Lynch, W. F., 267

Margolis, J., 850
Mark, G. E., Jr., 430
Marriott, H. J. L., 883
Massumi, R. A., 575
Mayo, M., 492
McCord, M. C., 210
McDermott, T. F., 512
McIntosh, H. D., 875
Meadows, W. R., 903
Milch, L. J., 31
Misra, S. N., 373
Montgomery, H., 646
Moon, R. Y., 713
Morris, G., 379
Morris, L. E., 448
Morton, R. F., 897
Moyer, J. H., 379
Murray, J. F., 547

Neill, E. C., 713
Noble, N. L., 366
Nordenström, B., 682
Nydick, I., 324

O'Neal, R. M., 64, 197

Page, E. B., 721
Papp, C., 105
Pappas, E. G., 525
Paul, O., 757
Pemberton, A. H., 568
Phythyon, J. M., 385
Pick, A., 603
Pontius, R., 379
Porfido, F. A., 512
Prinzmetal, M., 575
Pryor, W. W., 721

Rabin, E. R., 64, 197
Rammelkamp, C. H., 154
Redisch, W., 518
Reeves, T. J., 111
Roberts, B., 483
Rodbard, S., 850
Rogers, W. R., 434
Roller, J., 855
Romans, W. E., 897
Rose, J. C., 512
Rosenbaum, M. B., 82
Ruble, P. E., 397
Ruegsegger, P., 324

Sabiston, D. C., Jr., 14
Sanghvi, L. M., 373
Schick, A. F., 757
Schwedel, J. B., 267
Scrimshaw, N. S., 805
Selzer, A., 865
Semenson, C., 502
Sharma, R., 373
Siegel, A., 251
Sieker, H. O., 721
Sloan, H., 682
Smith, K. S., 827
Soloff, L. A., 430
Stamer, J. P., Jr., 682
Stare, F. J., 805
Steele, J. M., 118, 518
Steinberg, D., 391

Stollerman, G. H., 267
Stowell, E. C., Jr., 492
Ström, G., 5
Surawicz, B., 90, 98
Swan, H., 814

Tangco, F. F., 518
Taussig, H. B., 631
Taylor, C. B., 757
Tejada, C., 805
Thomas, J., 385
Thomas, W. A., 64, 197
Trulson, M., 805

Udenfriend, S., 353
Uricchio, J. F., 525

van Elk, J., 814
Van Goor, H., 54
Van Nieuwenhuizen, C. L. C., 54
Vander Veer, J. B., 713
Victor, M., 836
von Euler, U. S., 5
Voskian, J., 855

Wainfeld, B., 426
Wakerlin, G. E., 1
Walker, W. J., 31
Warren, J. V., 321, 875
Wasserman, F., 591
Watanabe, R., 502
Weiner, M., 353
Weiner, N., 31
Weinstein, L., 735
Weissler, A. M., 875
Wertheimer, L., 518
White, P. D., 915
Whittemore, R., 631
Wilson, G. P., 280
Wittels, B., 434
Wood, E. H., 568
Wróblewski, F., 324

Yarvis, J. J., 426
Young, D., 267

Zatuchni, J., 430

INDEX OF SUBJECTS

(Page numbers in italics refer to abstracts)

Acetazolamide
renal lesions after, *140*
thrombocytopenia after, *304*
Acetylcholine
atrial fibrillation from, *301*
in epinephrine arrhythmias, *472*
Acetyl-digitoxin, effects of, *474*
Acetyl strophanthidin therapy, *948*
ACTH and cortisone, in rheumatic fever, 225–229, *309*, *615*
in children, *616*
streptococcal antihyaluronidase and antistreptolysin titers after, *309*
Adrenal cortex
in diabetic retinopathy, *781*
effects of renal hemodynamics, *952*
steroids, cardiotonic activity of, *947*
Adrenalism, hyperactive, from steroid therapy in rheumatic fever, 225–229
Adrenergic blocking drugs, 47–53
Age factors in hemoglobin level in congenital heart disease, *133*
Aging
arrhythmia after thoracic surgery, *144*
arterial, and hypertension, 827–834
drug effects in, *949*
metabolic responses in cold environment, *313*
peripheral vein diseases, *791*
vascular skin lesions, *619*
Airsickness, and head immobilization, *314*
Aldolase level in myocardial infarction, *942*
Aldosteronism
from adrenocortical hyperplasia, *781*
and arterial hypertension, *467*
Alkalosis, respiratory, potassium elevation in, *951*
Allergic heart disease, *794*
Altitude, effects of, *313*
Alveoli
oxygen tension, and arterial oxygen saturation, *314*
pulmonary, studies in mouse, *468*
walls in mitral stenosis, 64–67
American Heart Association
annual report (1956), 624
applications for research support, 956
Arteriosclerosis Society
abstracts, 477
new officers, 151
award winners, 625–630
awards, 624
Blakeslee award entries, 476
California fellowships, 477
cardiovascular research training program, 151, 476
Conference proceedings published, 624
congenital cardiac defects, 631–638
Denver fellowship in cardiopulmonary physiology, 797
electrocardiographic interpretation course, 956
fellowships and research grants available, 150
Ferris appointment, 476
film of heart beat disorders, 316
Heart Fund (1957), 150
High Blood Pressure Council leaders, 317
Inter-American Medical Convention in Panama, 477
leaflet for hypertensives, 316
London Harvey Tercentenary, 151, 796
meetings calendars, 152, 317, 624, 798, 957
Michigan conference on hypertension, 624
National Health Forum, 151
National Office, 796
New materials issued, 796
Ohio fellowships, 477
physicians honored, 317
rheumatic fever prevention, 316
Scientific Sessions (1956), 317
Scientific Sessions (1957), 316, 476
commemorating William Harvey, 795
memorial lecturers for, 956
UN statements on radiation effects, 477
Utah Heart Association, 317
Wisconsin Conference on Work and Heart, 150, 797
World Conference in Brussels, 152
Aminopherase. *See* Transaminase
Aminophylline
in circulation time studies, 451
effects of, 113
rectal, plasma theophylline after, *949*
Amniotic fluid, fatal pulmonary embolism from, *468*
Amyl nitrite, in circulation time studies, 451
Anaphylactic heart lesions, experimental studies, *303*
Anastomoses, comparison of methods, *144*
Anemia
cardiovascular disturbances in, 373–377
circulation time in, 456
Anesthesia
digitalis with, *305*
dolitrone, effects of, *305*
heart sounds in, *138*
hemodynamic effects of, *301*
hypotensive technics, *143*, *617*
hypothermia. *See* Hypothermia
Aneurysms
aortic, *141*, 483–490
abdominal, 483
and right renal artery, surgery in, *148*
arch, total excision in, *145*
ascending, fusiform aneurysm, *790*
dissecting, *618*
healed, 540–545
shock in, *955*
excision of, *145*, *310*
sinuses, syphilitis, *620*
thoracic, 485
with giant-cell arteritis, hormone therapy in, *148*
renal arteriovenous, *149*
splenic arterial, ruptured, in parturition, *149*
Angina pectoris
changing patterns in, *943*
choline theophyllinate therapy, *943*
in myocardial infarction, 199
therapeutic agents, 405–412
U wave in, 106
Anginal pain, in pulmonic stenosis, 258–265
Angiocardiography
in cor triloculare biatriatum, 707
in intrathoracic tumors, *616*
in left-to-right shunts, *952*
in mitral and aortic insufficiency, *784*
percutaneous, of aorta, *149*
and polytomography, *953*
Angiography
cerebral, *952*
complications during, *146*
renal, tolerance to contrast media in, *616*
Angiosarcoma, pericardial, *141*
Anoxia, neurologic tolerance to, *306*
Anxiety, consequences of, *313*
Aorta
aneurysms. *See* Aneurysms, aortic
atherosclerotic, lipoproteins extracted from, *936*
calcification in syphilis, *784*
coarctation
and congestive failure, in infancy, *133*
electrocardiogram in hypertension with, *940*
depressor reflexes from nerve fibers, *949*
dilatation index, *310*
emboli, fibrinolytic enzymes affecting, *145*
insufficiency. *See* Insufficiency, aortic
intima
studies in atheroma, 366–371
trauma, cholesterol affecting tissue repair, *610*
percutaneous angiocardiography of, *149*

Aorta (*Cont'd*)
stenosis. *See* Stenosis, aortic
thoracic
obstruction of, collateral circulation in, *148*
surgery of, hypothermia and hypotension in, *143*
valvular disease, *471*, 930
valvuloplasty, 932–934
vascular grafts, *617*
Aortic arch
coarctation, resection of, blood pressure changes in, *296*
experimental replacement of, *311*
thrombotic obliteration of branches, 237–244
Aortico-coronary sinus anastomosis, effects of, *940*
Aortico-pulmonary defect, congenital, closure under refrigeration, *311*
Aortography, thoracic, with radiopaque polythene catheter, *616*
Apresoline therapy in hypertension, *779*
Arctic climate affecting electrocardiogram, *464*
Arm, tired arm syndrome, *794*
Arrest, cardiac, treatment of, *307*, 594
Arrhythmia
digitalis glycoside in, first heart sound after, *308*
electric and mechanical systoles in, *135*
in older age group, after thoracic surgery, *144*
procaine amide in, 120–122
Arteries
aging of, and hypertension, 827–834
carotid cavernous fistulas, *618*
coronary
anomalous, *461*
in aortic stenosis, 933
arteriography, *616*
changes after aortico-coronary sinus anastomosis, *940*
changing patterns in angina pectoris, *943*
cholesterol, diet, and racial factors in disease, *135*
diabetic cardiac patient, *134*, *297*
hexamethonium in insulin-induced hypoglycemia and angina pectoris, *613*
myocardial infarction. *See* Infarction, myocardial
myocardial ischemia with, *612*
pressure, *782*
sclerosis in younger age group, *612*
serologic tests for inflammation, *297*
surgery in, *311*
transaminase activity in disorders, *134*, 324–333, *613*, *941*
U wave in disorders, 105–110
grafts. *See* Grafts
hepatic, inflow in hemorrhagic shock, *950*
mesenteric, inflow in hemorrhagic shock, *950*
occlusion, acute, *791*
oxygen saturation and alveolar oxygen tension, *314*
pressure. *See* Blood pressure, arterial
pulmonary
absent, in Fallot's tetralogy, *938*
atresia, in Fallot's tetralogy, *939*
in cor triloculare biatriatum, 708
distensibility in mitral stenosis, *789*
pressure in mitral stenosis, 430–433
stenosis. *See* Stenosis, pulmonary, arterial
thrombosis, *146*
and chronic cor pulmonale, *145*, *147*
weight of, in sclerosis and hypertension, *468*
renal
aortic homografts, *786*
percutaneous catheterization of, *149*
right renal, in aneurysm of abdominal aorta, *148*
subclavian, carotid-body-like tumor of, *792*
wall movements in atrioventricular block, *139*
Arteriography
coronary, *616*
intra-arterial Diodrast and Urokon in, *472*
Arteriosclerosis. *See* Atherosclerosis
Arteriovenous
fistulas
acquired, surgery in, *954*
of renal vessels, *149*
shunts in lung, *301*
Arteritis
giant-cell
with aneurysms, hormone therapy in, *148*
of legs, *148*
obliterative
brachiocephalic, 845–849
in supra-aortic trunks in young women, *147*
Artificial kidney, 285–293
Aschoff-body-like granulomata, induction of, *303*
Asthma
bronchial, circulation time in, 455
cardiac, pulmonary function in, 492–500
Atheroma, aortic intima studies in, 366–371
Atheromatous emboli, and renal hypertension, *465*
Atherosclerosis, *146*
arterial homografts in, 21–29
ausculatory gap in, 850–853
beta-lipoprotein levels in, 31
cholesterol levels. *See* Cholesterol
fat emulsion infusion studies, *609*, 889–895
idiopathic hyperlipemia with, *937*
infantile, *936*
lipoprotein metabolism after radiation, *609*
lipoproteins extracted from aortas, *936*
of lower limbs, grafts in, *145*
in myeloma, *620*
pathogenesis, *609*
sodium 2-phenylbutyrate in, *937*
Atria
dissociation, 883–887
fibrillation. *See* Fibrillation atrial
left atrial volume in mitral stenosis, 430–433
movements in mitral disease, *616*
pressure, and pulmonary vascular changes, *949*
pressure pulses in mitral valvular disease, *470*
septal defect, 186–191, *940*
in adults, 186
closure of, left ventricular failure after, 568–573
in infants and children, 191
pressure relationships after closure of, 568–573
triatrial heart, surgery in, *954*
uniatrial fibrillation, 883–887
Atriomegaly, extreme bilateral, 434–440
Atrioseptopexy, *787*
Atrioventricular
arrhythmia
mechanism, *469*
premature beats, *462*
block
arterial wall movements in, *139*
sodium lactate in, 591
tricuspid valve closure in, *138*
Audiovisual perception of cardiac vibrations, 481–482
Ausculatory gap in arteriosclerotic heart disease, 850–853
Axillary vein occlusion, anticoagulants in, *312*
Ayerza's disease, 35
Azapetine, effects of, 48

Ballistocardiography
aperiodic, as function of age, *944*
cigarette test, *462*
compared to phonocardiogram, *777*
elongation, *298*
measure of fidelity, 280–284
preoperative, 943
in valvular heart disease, *138*
Beck operations for coronary heart disease, *310*
Benzodioxane test for pheochromocytoma, 9
Beta-lipoproteins
dietary carbohydrates affecting, *619*
differential effects on, 31–33
Biopsy, pericardial, in diagnosis of pericarditis, *778*
Blood coagulation
anticoagulants in idiopathic occlusion of axillary vein, *312*

coagulability and thrombosis, *296*
fats affecting, 274–278
hemolytic reaction after intravenous mephyton, *133*
hemophilia, *938*
hemorrhagic thrombocythemia, *938*
platelet serotonin content factors, 353–356
proconvertin test, *296*
vitamin K_1 in hypoprothrombinemia, *938*
warfarin sodium, in anticoagulant therapy, *938*

Blood flow
coronary
and cardiac contraction, 14–19
cigarette smoking affecting, 251–256
metabolites affecting, *304*
pulmonary, increased, with pulmonary stenosis, *296*
renal, erythrocytes in regulation of, *783*
velocity, in health and disease, 448–457

Blood pressure
arterial
determination of in lower extremity, *147*
in hypothermia, 514
changes after resection of aortic arch coarctation, *296*
coronary, *782*
hypertension
aging of arteries in, 827–834
and aldosteronims, *467*
anti-hypertensive procedures, *140*
antiserotonins in, *779*
and aortic coarctation, electrocardiography in, *940*
Apresoline therapy, *779*
and cardiovascular disease, *465*, *466*
cerebral, *140*
and Conn's syndrome, *780*
genetic factor, *779*
in hemorrhagic fever, 418–420
L. E. cells in hydralazine disease, *466*
mecamylamine therapy, *946*, *947*
negative U waves in, 98–101
pathogenesis of, 1–3
pentolinium therapy, *467*
in pheochromocytoma, *946*
in poliomyelitis, *741*
pulmonary, 35–45, *134*
weight of pulmonary artery in, *468*
rauwolfia therapy, *465*, *946*
renal
and atheromatous embolization, *465*
response to pentolinium, *466*
two kinds of, *466*
rescinnamine therapy, *779*
reserpine therapy, *779*, *946*
with hydralazine therapy, *467*
total exchangeable sodium in, *465*
treatment, studies of, *464*
hypotension
metaraminol therapy, *782*
postural, treatment of, *791*
hypotensive anesthesia technics, *617*
pulmonary
experimental, by pulmonary embolization, *301*
hypertension, 35–45, *134*, *468*
in mitral disease, *142*, 430–433
wedge pressure, factors in, *143*

Blood vessels. *See* Arteries, Vascular conditions *and* Veins

Blood volume
hypervolemia, relative, in hemorrhagic fever, 422
in hypothermia, 514
left atrial, in mitral stenosis, 430–433
volumogram and electrogram, *469*

Book reviews
Cardiac Auscultation (Butterworth et al.), 771
Cardiac Diagnosis (Rushmer), 772
Cardiovascular Innervation (Mitchell), 774
Cardiovascular Surgery (Lam, Ed.), 77
Cerebral Vascular Disease (Luckey, Ed.), 774
Congenital Malformations and Vascular Tumors of Extremities (Martorell and Salleras), 132
Diagnosis of Congenital Heart Disease (Kjellberg et al.), 771
Electrocardiographic Test Book (Winsor, Ed.), 131
Le Foie et la Veine Porte (Albot et al.), 132
High Blood Pressure (Pickering), 130
Interpretation of Unipolar Electrocardiogram (Myers), 770
Life Stress and Essential Hypertension (Wolf et al.), 772
La Parte Finale del Ventricologramma e la Sindrome del Muscoli Papillari (Furbetta et al.), 771
Principles of Renal Physiology (Smith), 131–132
Die Thromboembolischen Erkrankugen und ihre Behandlung (Noegeli et al.), 129
Thrombosis and Embolism (Koller and Merz, Eds.), 131

Books received, 127–129

Brachiocephalic arteritis, obliterative, 845–849

Bradycardia, sinus, sodium lactate in, 591

Brown Memorial Lecture, 646–658

Buerger's disease, treatment of, *312*

Burger triangle, determination of, *299*

Calcium gluconate, in circulation time studies, 451

Calphyllin, in angina, 405–412

Cancellation of esophageal electrocardiograms, 897–902

Cancer of lung, and cigarette smoking, *793*

Capillaries, pulmonary, studies in mouse, *468*

Carbohydrates, dietary, effects of cholesterol and beta-lipoproteins, *619*

Carbon dioxide
in circulation time studies, 452
in tachycardia from veratrine, *473*

Carcinoma, bronchogenic, intracardiac extension of, *955*

Cardiograms in stenosis of great vessels, *776*

Cardiovascular
disorders
in anemia, 373–377
case progress index, *623*
in hypertension, *465*, *466*
in poliomyelitis, 735–754
return to work after, *793*
function
in hypothermia, 512–516
knowledge of, before and after William Harvey, 726–733, 915–923

Carnigen, muscular pressure after, *305*

Carotid-body-like tumor of subclavian artery, *792*

Carotid cavernous fistulas, *618*

Catheterization
cardiac, in cor triloculare biatriatum, 707
left heart
percutaneous, *622*
preoperative, *470*
technic, *621*
percutaneous, of renal artery, *149*
right heart, ventricular fibrillation in, *473*

Causalgia, diagnosis and treatment of, *791*

Cedilanid
in arrhythmia, first heart sound after, *308*
effects on sodium and potassium balance, *783*

Cerebral
blood flow in polycythemia vera, *782*
circulation, measured by Evans blue dye, *306*
embolus, laterality of, *312*
hypertensive disease, chronic, *140*
lesions, electrocardiography in, *776*
metabolism, morphine and nalline affecting, 379–383

Chemoreceptors in blood vessels of ear of rabbits, *309*

Chest pain in isolated pulmonic stenosis, 258–265

Chiari syndrome in childhood, *792*

Cholesterol
and atherosclerosis, 31, *146*, *610*
and coronary heart disease, *134*

Cholesterol (*Cont'd*)
dietary carbohydrates affecting, *619*
dihydrocholesterol feedings in birds, *148*
effects on intimal repair of aorta after trauma, *610*
essential familial hypercholesterolemia and xanthomatosis, *937*
and lipoprotein concentrations, 805–812
metabolism studies, *610*
neurotropic drugs affecting, *937*
nicotinic acid affecting, *937*
nicotinic acid in hypercholesterolemia, and blood lipid changes, *936*
phenylbutyrate and phenylvalerate affecting, 391–395
reduction by brain extract administration, *619*
sitosterol in hypercholesterolemia, *937*
Choline theophyllinate therapy in angina pectoris, *943*
Chorea, and streptococcal infections, *614*
Cigarette smoking
ballistocardiographic test, *462*
effects on blood composition, *947*
effects on circulation, *302*
effects on coronary blood flow and myocardial metabolism, 251–256
and lung cancer, *793*
Cinematography of cardiac valves, *784*
Circulation
collateral, in obstruction of thoracic aorta, *148*
knowledge of, before and after William Harvey, 726–733, 915–923
peripheral, in valvular heart disease, *312*
pulmonary, 166–171
effects of pulmonary embolism, *301*
time studies, *951*
time
Decholin test of, 245–250
in hypothermia, 514
studies of, 448–457
Climate, arctic, affecting electrocardiogram, *464*
Clubbing, idiopathic, with hypertrophic osteoarthropathy, *620*
Coarctation of aorta, *133, 296, 940*
Cold environment, metabolic responses of old people in, *313*
Collateral circulation in acute obstruction of thoracic aorta, *148*
Commissurotomy, 924–932
in aortic stenosis, *310*
mitral
follow-up studies, *954*
indications for, in stenosis, *789*
staphylococcal endocarditis after, *295*
streptococcal infection after, 267–272
postcommissurotomy syndrome, 203–209, 267, *787*
transaortic, *786*
Congenital anomalies
absence of pulmonary valve, 397–403
absent left pulmonary artery in Fallot's tetralogy, *938*
age factors in hemoglobin level in congenital disease, *133*
aortico-pulmonary defect, closure under refrigeration, *311*
atrial septal defect, *940*
atypical patent ductus arteriosus, *133*
bicuspic pulmonary valve, *296*
blood pressure changes after resection in aortic arch coarctation, *296*
causes and prevention of defects, *611*
circulation time in, 455
coarctation of aorta with congestive heart failure in infancy, *133*
cor triloculare biatriatum, 701–711
coronary artery anomalies, *461*
Crafoord-Gross operation for isthmic stenosis of aorta, *133*
Decholin test in diagnosis, *611*
dextroposition of heart, *611*
diagnostic features of Ebstein's disease, *939*
differential diagnosis of dextracardia, *939*
Ebstein's disease, *461*
electrocardiogram in hypertension with aortic coarctation, *940*
etiology, *133*
homeostatic aspects of congenital disease, *939*
hydrodynamics in ventricular septal defects, *461*
isolated mitral stenosis, 348–364
multiple stenosis of pulmonary arteries in hypertension, *134*
occlusion of pulmonary vessels in hypertension with patent ductus arteriosus, *134*
peripheral rheograms, *940*
in pregnancy, 628
premature obliteration of foramen ovale, *938*
protection against bacterial endocarditis, 636
pulmonary atresia in Fallot's tetralogy, *939*
pulmonary stenosis with increased pulmonary blood flow, *296*
pulmonary vascular pathology in, 164–192
pulmonary venous drainage anomalies, *610*
pulmonary vessels in patent ductus arteriosus, *134*
report of committee, 631–638
valvular pulmonary stenosis, 814–825
vectorcardiography in diagnosis of, *138*
ventricular septal defect, *297, 611*
Conner Memorial Lecture, 164–192
Conn's syndrome with hypertension, *780*
Cooling, chest wall, effects of, 559–566
Cor pulmonale
and chronic pulmonary emphysema, 757–768
coronary blood flow in, *782*
massive arterial hemorrhage in, *313*
physiologic pathology, *302*
from pulmonary arterial thrombosis, *145, 147*
Cor triloculare biatriatum, 701–711
Coronary
arteries. *See* Arteries, coronary
dilator drugs, symposium, 111–117
sinus rhythm, electrocardiography in, *138*
Cortisone
and ACTH in rheumatic fever, *615*
in idiopathic pericarditis, *778*
after mitral valve surgery, *144*
in rheumatic fever, 225–229
Crafoord-Gross operation with graft, in aortic stenosis, *133*
Curare, respiratory arrest from, circulation in dogs after, *142*

Decholin test
in circulation time studies, 245–250, 452
in diagnosis of congenital defects, *611*
Dextracardia, differential diagnosis of, *939*
Diabetic cardiac patient, *134*
adrenal cortex in retinopathy, *781*
degenerative vascular disease in, *147*
and myocardial infarction, *297*
Diamox
renal lesions after, *140*
thrombocytopenia after, *304*
Dibenamine test for pheochromocytoma, 9
Dibenzyline, 49
in causalgia, *791*
Diet
in coronary heart disease, *134*
fats affecting blood coagulation, 274–278
sodium restriction, pressor effects of norepinephrine after, 231–236
Digitalis
in anesthesiology, *305*
in arrhythmia, first heart sound after, *308*
effects of, *473*
on electrocardiogram, 603–608
Dihydrocholesterol, arteriosclerosis from, in birds, *148*
Dilator drugs, coronary, symposium, 111–117

Diodrast, intra-arterial, vascular responses to, *472*
Diuretics, *305*
electrolyte excretion in, *951*
in pregnancy, 855–858
Dolitrone anesthesia, effects of, *305*
Ductus arteriosus, patent, 184–186
anomalous coronary artery simulating, *461*
atypical, *133*
pulmonary vessels in, *134*
surgical closure of, *953*
ventricular septal defect simulating, *297*
Dyspnea in myocardial infarction, 200

Ebstein's disease, 210–223, *461*
diagnostic features of, *939*
Edema, pulmonary
in hemorrhagic fever, 423
in poliomyelitis, 742
Eisenmenger complex, 172
Electrocardiography, 801–804
arctic climate effects, *464*
arterial wall movements in A-V block, *139*
in atrial dissociation, 883–887
benign bundle-branch block, *464*
in cardiac tamponade, *137*
in cerebrovascular lesions, *776*
in cooling of chest wall, 559–566
in cor triloculare biatriatum, 706
in coronary sinus rhythm, *138*
correlated with volumogram, *469*
diagnostic errors, *945*
digitalis affecting, 603–608
electric and mechanical systoles in arrhythmias, *135*
electric center of ventricular depolarization, *463*
ergotamine test in rabbit, *775*
esophageal atrial cardiograms, *140*
esophageal, cancellation of, 897–902
experimental production of Wolff-Parkinson-White syndrome, *136*
high anterior area
in normotensive subjects, 586
QRS complex, 586
ST segments, 587
T waves, 587
horizontal bipolar thoracic leads, *464*
in hypertension with aortic coarctation, *940*
jugular venous pulse registration, *945*
with kinetocardiography, 114
lead vectors and Burger triangle in normal subjects, *299*
left axis shift on assumption of upright position in children, *299*
in left ventricular hypertrophy with conduction delay, *298*
left ventricular strain pattern, 101
mass surveys, *462*
in myocardial infarction, 575
in poliomyelitis, 738
premature beats in atrioventricular rhythm, *462*
premature beats in supernormal phase of intraventricular conduction, *464*
Pro-banthine affecting, *945*
QRS complex
in myocardial infarction, *945*
prolongation, *776*
Q-T interval variations, *137*
quinidine affecting, *463*
R wave and T wave correlations, *463*
relative value of, *299*
T waves, 70–76, 90–97, *139*
TU-U abnormalities, 102–104
U waves, symposium, 70–110
in valvular pulmonary stenosis, 816
ventricular fibrillation with T wave inversion in A-V block, *139*
ventricular repolarization, *944*
Wolff-Parkinson-White syndrome, *299*
Electrokymography of left heart in mitral insufficiency, 682
Electrolytes
effects on circulation and acute hyponatremia, *783*
estrogen affecting metabolism, *951*
excretion in sulfate diuresis, *951*
Electron microscopy of lung, *780*
Embolectomy, arterial, repeated *786*
Emboli
aortic, fibrinolytic enzymes in, *145*
atheromatous, and renal hypertension, *465*
cerebral, laterality of, *312*
peripheral, in mitral stenosis, 929
pulmonary
antenatal, *148*
diagnosis and management, *146*
experimental, *301*
fatal, by amniotic fluid, *468*
Emotions and cardiac symptoms, *313*
Emphysema, pulmonary
circulation time in, 455
and cor pulmonale, 757–768
coronary blood flow in, *782*
Encephalopathy, Wernicke's, 836–843
Endocarditis
bacterial
after cardiac surgery, 525–530
and congenital cardiac defects, 636
in mitral stenosis, 931
murmurless, 777
in poliomyelitis, 740
staphylococcal, 641–644
after mitral valvulotomy, *295*
subacute, *295*
penicillin V therapy, *295*
treatment of streptococcal infections in prevention of, 154–157
mycotic, of tricuspid valve, *778*
Endocrine effects on circulation, *140*
Eosinopenia in myocardial infarction, *942*
Epinephrine
arrhythmias from, acetylcholine in, *472*
plasma concentrations of, after chemical agents, *474*
Ergotamine test in rabbit, *775*
Erythrocyte packed cell volume determinations, *621*
Esophageal
atrial cardiogram, *140*
balloon tracings in mitral valve disease, *788*
electrocardiogram, cancellation of, 897–902
Estrogen, effects on water and electrolyte metabolism, *951*
Ether
anesthesia, hemodynamic effects, *301*
in circulation time studies, 452
Evans blue dye, measuring cerebral circulation, *306*
Exercise
in disease, respiratory function after, *469*
in gangrene of feet and legs, 689–700
tolerance test in mitral stenosis, *788*
Extrasystoles
electrically induced, *139*
ventricular, coupling intervals of, 82–89
Exudate, inflammatory, and anaphylactic tissue reaction, *303*

Fallot's tetralogy, 182
absent left pulmonary artery in, *938*
pulmonary atresia in, *939*
Fat emulsion infusion studies, 889–895
affecting serum lipoproteins, *609*
Fats, effects on blood coagulation, 274–278
Fetal pulmonary circulation, 167
Fibrillation
atrial
production in dogs, *301*
ventricular dynamics in, 335–346
uniatrial, 883–887
ventricular
procaine producing, *301*
in right heart catheterization, *473*
spontaneous reversion to normal rhythm in myocardial infarction, *297*
with T wave inversion in A-V block, *139*
Fibrosis, endocardial, in infants, *141*
Fistula, arteriovenous, acquired, surgery in, *954*

Fluorescein, in circulation time studies, 452
Foramen ovale, premature obliteration of, *938*

Gallop rhythm, 321–323
Gamma globulin in lesions of hypersensitivity states, *623*
Gangrene of feet and legs, ambulatory treatment, 689–700
Geriatric conditions. *See* Aging
Glucose in resuscitation of hypothermic heart, *781*
Glutamic oxaloacetic transaminase. *See* Transaminase
Glutathione, and cardiac muscle function, *307*
Grafts
aortic
and renal arteries, *786*
vascular, *617*
arterial, 21–29, *144*
and excision of aortic aneurysms, *310*
seamless synthetic, *785*
in atherosclerosis of lower limbs, *145*

Hamartoma, fibroelastic, of heart valves, *141*
Hand, numbness, in tired arm syndrome, *794*
Harvey, William
cardiovascular knowledge before and after time of, 726–733, 915–923
commemoration, 795
Head immobilization, and airsickness, *314*
Heart
arrest, treatment of, *307*, 594
beat, premature
in atrioventricular rhythm, *462*
in supernormal phase of intraventricular conduction, *464*
block
benign bundle-branch block, *464*
bundle branch, with myocardial infarction, vectorcardiography in, *777*
ventricular arrhythmias in, 547–557
contraction, and coronary blood flow, 14–19
dextroposition of, *611*
ejection curve, *308*
failure, congestive
circulation time in, 454
in infancy, with coarctation of aorta, *133*
function test, 54–63, *950*
in increased work, *302*
muscle function, and glutathione, *307*
Nylin function test, *950*
output
estimation, *309*
factors in, 875–882
Starr method, *313*
rate, effects of, *950*
sounds
in anesthesia, *138*
first, after digitalis glycoside in arrhythmia, *308*
in mitral stenosis, *614*
vibration analysis of, *139*
tamponade, electrocardiogram in, *137*
vascular system, *780*
Heat exchange, vascular, in fins of whales, *309*
Hemiplegia, vasomotor responses in, 519
Hemoglobin levels in congenital heart disease, age factors in, *133*
Hemolytic reaction after intravenous mephyton, *133*
Hemophilia, *938*
Hemorrhage
gastric, and salicylate ingestion, *623*
massive arterial, in chronic cor pulmonale, *313*
Hemorrhagic fever, hemodynamic changes in, 414–424
Hemostasis, platelet serotonin content factors, 353–356
Heparin-activated clearing factor, 889–895
Heparin therapy in myocardial infarction, *298*
Hepatic vein thrombosis, *792*
Hepatitis, viral, myocarditis in, *468*
Hexamethonium
in causalgia, *791*
in insulin-induced hypoglycemia and angina pectoris, *613*
Hibernation, artificial, circulatory function in, *308*
Histamine
in circulation time studies, 452
test for pheochromocytoma, 9
Homografts, arterial, 21–29, *144*
Hydralazine
disease, L.E. cells in, *466*
therapy, with reserpine, in hypertension, *467*
Hydrodynamics in ventricular septal defects, *461*
Hyperchlorhydria from intravenous reserpine, *304*
Hypotensive technics in surgery, *143*, *617*
Hypothalamic pressor response, reserpine affecting, *475*
Hypothermia
cardiovascular function in, 512–516
and hypotension in surgery of thoracic aorta, *143*
studies in monkeys, *303*, *781*
in surgery, results with, *145*
ventricular fibrillation from, thiopental in, *474*
Hypothermic heart, glucose in resuscitation of, *781*
Hypoxia in athletes, heart changes in, *142*

Ilidar, 48–49
Inactivity and changes in great vessels, *779*
Infarction
myocardial, *135*, 197–201, *941*
in aortic atenosis, 933
bundle-branch block with, vectorcardiography in, *777*
in diabetes, *297*
eosinopenia, *942*
glutamic oxalacetic transaminase levels, 134, 502–510, 613
heparin therapy in, *298*
high anterior, 575–590
lactic dehydrogenase activity, *613*
management, *612*
mortality rates, *298*
pain distribution, 348–351
plasma enzyme activity in, *942*
prognostic factors, *942*
QRS complex, *945*
racial incidence in Cape Town, *134*
radioactive iodine clearance in, *942*
serum aldolase levels in, *942*
spontaneous reversion of ventricular fibrillation to normal rhythm in, *297*
tests in, *297*
U wave in, 106
pulmonary
diagnosis and management, *146*
glutamic oxaloacetic transaminase activity in, 324–333
in mumps, *620*
in poliomyelitis, 749
Insufficiency
aortic
angiocardiography in, *784*
in aortic stenosis, 933
rheoplethysmogram in, *790*
coronary
glutamic oxaloacetic transaminase activity in, 324–333
U wave in, 106
mitral
angiocardiography in, *784*
left heart studies, 682–687
purse-string operation, 661–680
pulmonary, after valvuloplasty, 820
Insulin-induced hypoglycemia and angina pectoris, hexamethonium in, *613*
Insurance mortality investigations, *620*
Iodine, radioactive, clearance in myocardial infarction, *942*
Ischemic work, response to in forearm, *782*
Isopropylnorepinephrine in ventricular arrhythmias, 555

Janus syndrome, *784*

Kidneys
angiography, tolerance to contrast media in, *616*
arteries. *See* Arteries, renal

artificial, 285–293
contraindications, 292
experimental use of, 292
indications for, 290–292
blood flow regulation, erythrocytes in, *783*
denervation, effects of, *783*
effects on circulation, *951*
hematocrit of intrarenal blood, *783*
hemodynamics, after pendiomide in hypertension, *306*
interstitial pressure, *472*
lesions after acetazolamide, *140*
lesions related to cardiac lesions, *303*
pentolinium affecting activity, *474*
reversible uremic states, *783*
vascular response to vasodepressor sympathomimetics, *472*
Kinetocardiography with electrocardiography, 114–117

Lactic dehydrogenase activity in myocardial infarction, *613*
Lead vectors, determination of, *299*
Lipase, lipoprotein, 889
Lipemia
idiopathic hyperlipemia with atherosclerosis, *937*
protamine in, *619*
Lipids
changes after nicotinic acid in hypercholesterolemia, *936*
metabolism studies, 889–895
Lipoma, vascular, with ophthalmoplegia, steatorrhea and phlebectasia, 792
Lipoproteins
beta-lipoproteins, 31–33, *619*
and cholesterol concentrations, 805–812
extracted from atherosclerotic aorta, *936*
lipase, 889
metabolism after radiation, *609*
Liver, and circulatory regulation, *315*
Lobeline, in circulation time studies, 452
Lungs
cancer, and cigarette smoking, *793*
circulation, 166–171
effects of pulmonary embolism, *301*
time studies, *951*
circulatory changes in mitral stenosis, 721–725
cor pulmonale. *See* Cor pulmonale
electron microscopy of, *780*
emphysema and cor pulmonale, 757–768
function tests, *314*
mechanical properties in orthopnea, 859–863
vascular diseases. *See* Vascular conditions, pulmonary
Lupus erythematosis
diagnostic procedures, *614*
neurologic and psychiatric signs in, *613*

Magnesium sulfate in circulation time studies, 452
Mammopathy, adolescent, in rhabdomyosarcoma of heart, *613*
Marfan's syndrome, 543
Mecamylamine therapy in hypertension, *946*, *947*
Mecholyl test for pheochromocytoma, 9
Mephyton, intravenous, hemolytic reaction after, *133*
Mercaptomerin, reactions to, *305*
Mercuhydrin, in pregnancy, 855
Mersoben
diuretic, *305*
in pregnancy, 855
Mesothelioma of pericardium, 385–389
Metabolic effects on circulation
cardiotonic activity of adrenal steroids, *947*
cigarette smoking, effects of, *947*
nutritional deficiency, *947*
responses of old people to cold environment, *313*
tocopherol intake, *947*
Metabolites affecting coronary flow and cardiac acitivity, *304*
Metamine in angina, 405–412
Metaraminol in hypotension, *782*
Metrox in pregnancy, 855
Mictine, evaluation of, 426–428
Mitral valve. *See* Valves, mitral
Mononucleosis, infectious, cardiac involvement in, *954*
Morphine, effects on cerebral metabolism, 379–383
Mortality rate
insurance investigations, *620*
in myocardial infarction, 298
review of medical cardiac deaths, *622*
in valvular pulmonary stenosis, 819
Mumps, pulmonary infarction in, *620*
Murmurs, vibration analysis of, *139*
Muscular pressure after carnigen injection, *305*
Myeloma, artherosclerosis in, *620*
Myocarditis
in poliomyelitis, 735–740
in viral hepatitis, *468*
Myocardium
cigarette smoking affecting metabolism, 251–256
failure, 930
idiopathic, in pregnancy and puerperium, 903–913
infarction. *See* Infarction, myocardial
ischemia with coronary artery disease, *612*
length of fibers and nuclei in cardiac dilatation, *467*
physiopathology, *780*
revascularization, *785*
sodium lactate in disorders, 591
Myxedema
circulation time in, 456
heart disease, *140*, 442–447
Myxoma
atrial, diagnosis of, *142*
mitral stenosis from, *955*

N-allylnormorphine, affecting cerebral metabolism, 379–383
Neohydrin, in pregnancy, 855
Nephrectomy, extracellular fluid after, *952*
Nephritis, epidemic acute, *314*
Nervous control of joint blood vessels, *793*
Neurosis, cardiac, *313*
Newborn, vectorcardiography of, *298*
Nicotinic acid, effects of
on blood cholesterol, *937*
on blood lipids, in hypercholesterolemia, *936*
Nicotine, effects of. *See* Cigarette smoking
Nitrites, effects of, 113, 116
Nitroglycerin, effects of, 113, 117
ointment, 116
sublingual, 114
Nitroglyn, effects of, 114
Norepinephrine, pressor effects of, after sodium restriction, 231–236
Nutritional deficiency, effects of, *947*
Nylin heart function test, *950*

Ophthalmoplegia, steatorrhea, phlebectasia and vascular lipomas, *792*
Orthopnea, mechanical properties of lungs in, 859–863
Osteoarthropathy, hypertrophic, idiopathic clubbing with, *620*
Oxygen
arterial saturation, and alveolar oxygen tension, *314*
tension of tissue in vivo, 646–658
uptake, maximal, *302*

Pacemaker
electric, in ventricular standstill, *776*
ultramicroelectrode recording from, *308*
Pain distribution in myocardial infarction, 348–351
Papaverine
in circulation time studies, 453
effects of, 113–114
Paraldehyde, in circulation time studies, 453
Pathologic physiology
atrial fibrillation production in dogs, *301*
changes of cardiac dynamics in mitral valvulvar disease, *300*
chronic cor pulmonale, experimental findings, *302*
circulation in dogs after respiratory arrest from curare, *142*

Pathologic physiology (*Cont'd*)
diagnosis of atrial myxomas, *142*
duration of diastole in mitral stenosis, *469*
dye dilution curves in valvular disease, *471*
effects of pulmonary embolism on pulmonary circulation, *301*
experimental pulmonary hypertension by embolization, *301*
heart in increased work, *302*
heart sensitivity to hypoxia in athletes, *142*
hemodynamic effects of ether anesthesia, *301*
hypothermia in monkeys, *303*
inflammatory exudate and anaphylaxis, *303*
mechanism of atrioventricular arrhythmias, *469*
oxygen uptake, maximal, *302*
preoperative left-heart catheterization, *470*
pressure curves from coronary sinus, *470*
pressure patterns in constrictive pericarditis, *470*
pressure pulses in aortic valvular disease, *471*
pressure pulses in mitral valvular disease, *470*
pulmonary arterial wedge pressure, *143*
pulmonary capillary pressures in mitral disease, *142*
relation of volumogram and electrogram, *469*
renal lesions related to cardiac lesions, *303*
respiratory function in disease, after exercise, *469*
thoracic duct ligation and anaphylaxis, *303*
vasoactive drugs and oxygen saturation of coronary sinus blood, *300*
woman without pulse, *302*
work hypertrophy of heart in rats, *300*
Pathology
aneurysms of aorta, *141*
electron microscopy of lung, *780*
endocardial fibrosis in infants, *141*
fatal pulmonary embolism by amniotic fluid, *468*
fibroelastic hamartomas of heart valves, *141*
inactivity and changes in great vessels, *779*
measurements of ventricles in hypertrophy, *141*
muscle fiber measurements in cardiac dilatation, *467*
myocarditis in viral hepatitis, *468*
pericardial angiosarcoma, *141*
pneumocardiopexis in revascularization of heart, *468*
pulmonary capillaries and alveoli of mouse, *468*
renal lesions after acetazolamide, *140*
secondary vascular changes in lungs, *780*
weight of pulmonary artery in sclerosis and hypertension, *468*
Pendiomide in hypertension, renal hemodynamics after, *306*
Penicillin
in prophylaxis for bacterial endocarditis in congenital defects, 637
in streptococcal pharyngitis in children, *615*
Penicillin V
clinical uses, *473*
in subacute bacterial endocarditis, *295*
Pentaerythrol tetranitrate, effects of, 114
in angina, 405–412
Pentolinium in hypertension, *467*
renal response to, *466*, *474*
Pericarditis
acute nonspecific, *777*
circulation time in, 455
constrictive, 161–163
pressure patterns in, *470*
diagnosis by pericardial biopsy, *778*
glutamic oxaloacetic transaminase activity in, 324–333
idiopathic, cortisone in, *778*
in poliomyelitis, 740
Pericardium
effusion in scleroderma, *955*
mesothelioma of, 385–389
transaminase levels in injury, *778*
Peripheral circulation disturbances in valvular heart disease, *312*
Peritrate
in angina, 405–412
effects of, 114
Pharmacology
acetazolamide, *304*
acetylcholine in epinephrine arrhythmias, *472*
acetyl-digitoxin, *474*
acetyl strophanthidin therapy, *948*
antiserotonin agents, *472*
carbon dioxide in tachycardias from veratrine, *473*
cardiac arrests, treatment of, *307*
carnigen, intramuscular pressure after, *305*
catheterization. *See* Catheterization
digitalis in anesthesiology, *305*
digitalis glycoside in arrhythmia, *308*
digitalization, effects of, *473*
Diodrast and Urokon, intra-arterial, in arteriography, *472*
Dolitrone, effects of, *305*
drug effects in aging patients, *948*
epinephrine, plasma concentrations after chemical agents, *474*
Evans blue dye measuring cerebral circulation, *306*
glutathione and cardiac muscle function, *307*
hibernation, circulatory function in, *308*
mercaptomerin, reactions to, *305*
mersoben as diuretic, *305*
metabolites, action on heart, *304*
mitral valve function, *306*
pendiomide in hypertension, renal activity after, *306*
penicillin V, *473*
pentolinium affecting renal activity, *474*
pneumomassage of heart, *471*
procaine amide and quinidine, and heart action, *304*
renal interstitial pressure, *472*
reserpine and hypothalamic pressor response, *475*
reserpine, intravenous, hyperchlorhydria from, *304*
resuscitation and neurologic tolerance to anoxia, *306*
ronicol, effects of, *948*
Sintrom, 713–719
Strophanthin affecting heart action, *305*
Strophanthin and renal excretion of potassium and sodium, *473*
succinylcholine in cardiac synapses, *949*
theophylline, plasma, after rectal aminophylline, *949*
thiopental in ventricular fibrillation from hypothermia, *474*
tolazoline, arrhythmias from, *472*
ultramicroelectrode recording from cardiac pacemaker, *308*
vasodepressor sympathomimetics, renal vascular response to, *472*
venomotor tone in venous congestion, *307*
veratrum and rauwolfia, mixture, effects of, *304*
Phenoxybenzamine, 49
Phenoxymethyl penicillin, *473*
in subacute bacterial endocarditis, *295*
Phentolamine test for pheochromocytoma, 9
Phenylbutazone
in rheumatic fever, *310*
in thrombophlebitis, complications of, *312*
Phenylbutyrate
in atherosclerosis, *937*
in hypercholesterolemia, 391–395
Phenylvalerate activity in hypercholesterolemia, 391–395
Pheochromocytoma
diagnosis and treatment, 5–11
drug tests for, 9–10
hypertensive phase, *946*
localization of tumor, 10

Phlebectasia, ophthalmoplegia steatorrhea and vascular lipomas, *792*
Phlebothrombosis in poliomyelitis, 749
Phonocardiograms, *299*, 481
in children, *138*
compared to ballistocardiogram, *777*
Photoroentgenography, relative value of, *299*
Physical medicine, role of, *793*
Physiology
adrenal cortex in diabetic retinopathy, *781*
aldosteronism from adrenocortical hyperplasia, *781*
cardiac ejection curve, *308*
cardiac output estimation, *309*
cerebral blood flow in polycythemia vera, *782*
chemoreceptors in blood vessels of ear of rabbits, *309*
Conn's syndrome with hypertension, *780*
coronary flow in pulmonary emphysema and cor pulmonale, *782*
counter-current vascular heat exchanges in fins of whales, *309*
depressor reflexes from aortic nerve fibers, *949*
duration of isotonic systole, *950*
glucose in resuscitation of hypothermic heart, *781*
heart rate, effects of, *950*
hypothermia in monkeys, *781*
left atrial pressure and pulmonary vascular changes, *949*
mesenteric and hepatic artery flow in hemorrhagic shock, *950*
metaraminol in hypotension, *782*
new method for indicator-dilution curves, *949*
Nylin heart function test, *950*
pulmonary circulation time studies, *951*
responses to ischemic work in forearm, *782*
right ventricular contraction and coronary artery pressure, *782*
splenic nerve stimulation, *949–950*
succinic dehydrogenase activity after exercise, *951*
Plasma
clearing factor, heparin-activated, 889–895
enzyme activity in myocardial infarction, *942*
Platelet serotonin, and clotting and hemostasis, 353–356
Pneumonia, circulation time in, 455
Pneumocardiopexis in revascularization of heart, *468*
Pneumomassage of heart, *471*
Pneumothorax, circulation time in, 455
Poiseuille's law, 449
Polarographic measurement of oxygen tension, 650
Poliomyelitis, cardiovascular disorders in, 735–754
Polycythemia vera
cerebral blood flow in, *782*
circulation time in, 456
Polytomography and angiocardiograph, *953*
Positive-pressure breathing, intermittent, *621*
Postcommissurotomy syndrome, 203–209, 267, *787*
Postural hypotension, treatment of, *791*
Potassium
changes, in cooling of chest wall, 559–566
elevation in respiratory alkalosis, *951*
exchangeable content, after steroid therapy in rheumatic fever, 225–229
hyperpotassemia, sodium lactate in, 596
after mitral valve surgery, *144*
studies of, *783*
Pregnancy
comparison of bed rest and diuretics, 855–858
and congenital cardiac defects, *638*
idiopathic myocardial failure in, 903–913
mitral stenosis in, 931
toxemia of, *315*
Pressor effects of norepinephrine after dietary sodium restriction, 231–236
Pressure pulses
in aortic valvular disease, *471*
in hypothermia, 514
in mitral valvular disease, *470*
Pressures, intracardiac, registration of, *776*
Priscoline, 48
arrhythmias from, *472*
Priscoline-regitine, 49
Pro-banthine affecting electrocardiogram, *945*
Procaine amide, 118–124
action of, 118–119
administration of, 122
in arrhythmias, 120–122
disposition and fate of, 119
dosages, 122
effects on heart action, *304*
major uses of, 123–124
pharmacology, 119–120
relation to quinidine, 123
toxicity, 122–123
ventricular tachycardia and fibrillation from, *301*
Proconvertin test, *296*
Protamine, in lipemia, *619*
Prothrombin time, vitamin K_1 in hypoprothrombinemia, *938*
Psychiatric
complications of mitral surgery, *144*
signs in lupus erythematosus, *613*
Puerperium, idiopathic myocardial failure in, 903–913
Pulmonary
arteries. *See* Arteries, pulmonary
conditions. *See* Lungs
hypertension. *See* Blood pressure, hypertension, pulmonary
valves. *See* Valves, pulmonary
veins. *See* Veins, pulmonary
Pulse, woman without, *302*
Pulseless disease, 237
Purse-string suture of mitral ring, 661–680
Pyrimidinedione derivatives as diuretics, 426–428

Quinidine
action on heart, *304*
effects on electrocardiogram, *463*
relation to procaine amide, 123
Q-T interval variations, *137*

Racial incidence of myocardial infarction in Capetown, *134*
Radioactive iodine clearance in myocardial infarction, *942*
Radioactive sodium, in circulation time studies, 453
Radiopotassium dilution curves in mitral valvular disease, 532–538
Radium C, in circulation time studies, 453
Rauwolfia in hypertension, *465*
depression from, *946*
and veratrum, mixture, effects of, *304*
Raynaud's syndrome, treatment of, *312*
Refrigeration. *See* Hypothermia
Refusion, after mitral valvuloplasty, 931
Regitine test for pheochromocytoma, 9
Rehabilitation, role of, *793*
Renal conditions. *See* Kidneys
Repolarization, ventricular, *944*
Rescinnamine, in hypertension, *779*
Reserpine
effects on hypothalamic pressor response, *475*
in hypertension, *779*, *946*
with hydralazine, *467*
intravenous, hyperchlorhydria from, *304*
Respiration
artificial, circulatory changes in, 744
in left ventricular failure, 492–500
Respiratory function in disease, after exercise, *469*
Resuscitation, cardiac, *306*
of hypothermic heart, glucose in, *781*
time limit for, *623*
Revascularization of myocardium, *785*
pneumocardiopexis in, *468*
Rhabdomyosarcoma of heart, adolescent mammopathy in, *613*

Rheoangiograms after nitroglycerin, *775*
Rheograms
peripheral, in congenital heart disease, *940*
venous congestion in, 945
Rheoplethysmogram
in aortic insufficiency, *790*
digital, *944*
Rheumatic fever
antistreptolysin and streptococcal antihyalurondiase titers after hormone therapy, *309*
chemoprophylaxis in streptococcal infection, 154–157, *615*
chorea and streptococcal infections, *614*
cortisone and ACTH therapy, 225–229, *309*, *615*
in children, *616*
penicillin in streptococcal pharyngitis in children, *615*
prolonged steroid therapy for, 225–229
therapy, *310*
valvular lesions in, *614*
Rheumatic heart disease
and myocardial failure, 932
and postcommissurotomy syndrome, 203–209
Roentgenology
angiocardiography. *See* Angiocardiography
angiography. *See* Angiography
aortic calcification in syphilis, *784*
aortic dilatation index, *310*
aortography with radiopaque polythene catheter, *616*
arteriography, *472*, *616*
cinematography of cardiac valves, *784*
contrast examination of left heart in mitral insufficiency, 682
in cor triloculare biatriatum, 706
Janus syndrome, *784*
left atrial movements in mitral disease, *616*
polytomography and angiocardiograph, *953*
splenoportography, *952*
variations in horizontal diameter of heart, *784*
Ronicol therapy, effects of, *948*

Saccharin, in circulation time studies, 453
Salicylate ingestion, *623*
Scleroderma, pericardial effusion in, *955*
Sclerosis
coronary arteries, in younger age group, *612*
pulmonary artery, and weight of artery, *468*
Sedimentation rate determinations, *621*
Septal defects
atrial. *See* Atria, septal defects
ventricular. *See* Ventricular septal defects
Serotonin
antiserotonin agents, *472*
excess in hypertension, *779*
platelet, and clotting and hemostasis, 353–356
Shin splints, *794*
Shock
in dissecting aortic aneurysm, *955*
hemorrhagic, mesenteric and hepatic artery inflow in, *950*
in hemorrhagic fever, 416–418
in poliomyelitis, 746
Shoulder, frozen, management of, *793*
Sinoatrial block, periodic, experimental, *139*
Sintrom, evaluation of, 713–719
Sinus
aortic, syphilitic aneurysm of, *620*
cavernous, carotid cavernous fistulas, *618*
coronary, pressure curves from, *470*
Sitosterol in hypercholesterolemia, *937*
Smoking. *See* Cigarette smoking
Sodium
cyanide, in circulation time studies, 452
deficiency, and water and electrolyte distribution, *783*
lactate
indications and contraindications, 591–602
ventricular arrhythmias after, 547–557
levels, after mitral valve surgery, *144*
radioactive, in circulation time studies, 453
restriction, dietary, pressor effects of norepinephrine after, 231–236
Sounds. *See* Heart sounds
Spinal cord transection, vasomotor responses after, 519
Spleen, and circulatory regulation, *315*
Splenic
arterial aneurysm, ruptured, in parturition, *149*
nerve stimulation, 949–950
Splenoportography, *952*
Stab wound, of heart, activity after, *312*
Staphylococcal endocarditis, 641–644
after mitral valvulotomy, *295*
Starling's law, test of, 344
Starr method of cardiac output measurement, *313*
Steatorrhea, ophthalmoplegia, phlebectasia and vascular lipomas, *792*
Stenosis
aortic, 932-934
Crafoord-Gross operation with graft, *133*
surgery in, *785*
transaortic commissurotomy in, *786*
valvotomy in, *310*
mitral, *790*
alveolar walls in, 64–67
commissurotomy in, indications for, *789*
distensibility of pulmonary vessels in, *789*
duration of diastole in, *469*
duration of mechanical systole in, *788*
electron microscopy in, *780*
exercise tolerance test in, *788*
isolated congenital, 358–364
left atrial volume in, 430–433
from myxoma, *955*
presystolic murmur in, *789*
pulmonary circulation changes in, 721–725
purse-string operation for, 661–680
with record pulmonary capillary pressure, *788*
reduplicated second heart sound in, *614*
surgery in, *311*, 924
pulmonary
arterial
branch of artery, 865–873
with pulmonary hypertension, *134*
valvular, 814–825
chest pain in, 258–265
congential, 814–825
with increased pulmonary blood flow, *296*
tricuspid, *787*
rheumatic, *790*
Sternal puncture technic, *775*
Steroid therapy, prolonged, in rheumatic fever, 225–229
Stethoscopes, 481
Stokes-Adams attacks, sodium lactate in, 592
Streptococcal infections
antihyaluronidase and antistreptolysin titers after therapy in rheumatic fever, *309*
chemoprophylaxis in, 154–157, *615*
and chorea, *614*
after mitral commissurotomy, 267–272
pharyngitis in children, penicillin in, *615*
Strokes, little, *148*
Strophanthin therapy, *948*
affecting heart action, *305*
and renal excretion of potassium and sodium, *473*
Succinic dehydrogenase activity after exercise, *951*
Succinylcholine in cardiac synapses, *949*
Surgery
in aortic stenosis, *785*
aortic valvuloplasty, 932–934
in aortico-pulmonary defect, *311*
arrhythmia in older age group after thoracic surgery, *144*
arterial embolectomy, repeated, *786*
in arteriovenous fistulas, acquired, *954*
atrioseptopexy, *787*
Beck operation for coronary heart disease, *310*

by-pass, cardiac, with continuous perfusion from reservoir of oxygenated blood, *143*
commissurotomy. *See* Commissurotomy
in coronary artery disease, *311*
direct vision, with brain-cooling by irrigation, *786*
endocarditis after, 525–530
excision of aortic aneurysm, *145*, *310*
grafts. *See* Grafts
hypotensive anesthesia technics, *143*, *617*
hypothermia in, *143*, *145*
ligation of inferior vena cava, *953*
in mitral insufficiency, 661–680
in mitral stenosis, *311*
mitral valvuloplasty, 924–932
in patent ductus arteriosus, *953*
potassium and cortisone after mitral valve surgery, *144*
psychiatric complications of mitral surgery, *144*
in pulmonary stenosis, valvular, 814–825
in pulmonary venous drainage anomalies, *617*, *954*
replacement of aortic arch, *311*
revascularization of myocardium, *785*
thromboendarterectomy, *953*
in transposition of aorta and pulmonary artery, *953*
in triatrial heart, *954*
valvotomy. *See* Commissurotomy

Sympathectomy
in arteriosclerotic occlusive disease, 21
lumbar, *792*
vasomotor response after, 518

Syncope, vasodepressor, 875–882

Syphilis, aortic calcification in, *784*

Syphilitic aneurysm of aortic sinus, *620*

Systoles
electric and mechanical
in arrhythmias, *135*
duration in mitral stenosis, *788*
isotonic, duration of, *950*

T waves
fusion with U waves, 70–76
inversion, in ventricular fibrillation in A-V block, *139*
related to U wave, 90–97

Tachycardia
ventricular
in heart block, 554
procaine producing, *301*
from veratrine, carbon dioxide in, *473*

Takayasu disease, 845

Tamponade, cardiac, electrocardiogram in, *137*

Temperature
body, studies of, *309*
environmental, effects on electrocardiogram, *464*

Tetraethylammonium test for pheochromocytoma, 10

Tetralogy of Fallot, 182, *938*, *939*

Theophylline in plasma after rectal aminophylline, *949*

Thiamine, in circulation time studies, 453

Thiopental, in ventricular fibrillation from hypothermia, *474*

Thoracic
aorta
obstruction of, *148*
surgery of, *143*
duct ligation, and anaphylaxis, *303*
leads, horozontal bipolar, *464*
pain, in isolated pulmonic stenosis, 258–265

Thorazine, in angina, 405–412

Thrombin
activity, residual, test, of, 353
antithrombin test, 353

Thromboangiitis obliterans, *618*

Thrombocythemia, hemorrhagic, *938*

Thrombocytopenia after acetazolamide, 304

Thromboembolic phenomena
anticoagulants in axillary vein occlusion, *312*
complications of phenylbutazone in thrombophlebitis, *312*
cor pulmonale from pulmonary arterial thrombosis, *145*, *147*
effects of Sintrom, 713–719
intra-aortic fibrinolytic enzymes in aortic emboli, *145*
laterality of cerebral emboli, *312*
postoperative thrombophlebitis, *618*
pulmonary embolism and infarction, *146*
vitamin K_1 in hypoprothrombinemia, *938*

Thromboendarterectomy, *953*

Thrombophlebitis
phenylbutazone in, complications of, *312*
in poliomyelitis, 749
postoperative, *618*

Thrombosis
and coagulability, *296*
hepatic vein, *792*
inferior vena caval, *792*
obliterative, of branches of aortic arch, 237–244
of pulmonary arteries, *146*
and chronic cor pulmonale, *145*, *147*

Thyroid extract, atrial fibrillation from, *301*

Thyrotoxicosis, circulation time in, 456

Tobacco. *See* Cigarette smoking

Tocopherol intake requirements, *947*

Tolazoline, effects of, 48

Tolazoline-phentolamine, effects of, 49

Toxemia of pregnancy, *315*

Transaminase, serum
activity of, 324–333
determinations of, *941*
in diagnosis of myocardial infarction, *134*
in pericardial injury, *778*
significance of, 502–510

Trauma, cardiac, activity after stab wound, *312*

Tricuspid valve. *See* Valves, tricuspid

Trypsin, affecting aortic emboli, *145*

TU-U waves, terminal complex, abnormalities of, 102–104

Tumors, intrathoracic, angiocardiography in, *616*

U-waves, 70–110
in angina, 106–110
in coronary disease, 105–110
coupled ventricular extrasystoles in, 82–89
fusion with T waves, 70–76
genesis of, 77–81
in infarction, 105–106
in insufficiency, coronary, 106
negative, *136*
in hypertension, 98–101
normal limits of, *137*
related to cardiac cycle, *136*
related to T wave, 90–97
TU-U abnormalities, 102–104

Ultramicroelectrode recording from cardiac pacemaker, *308*

Uremia states, reversible, *783*

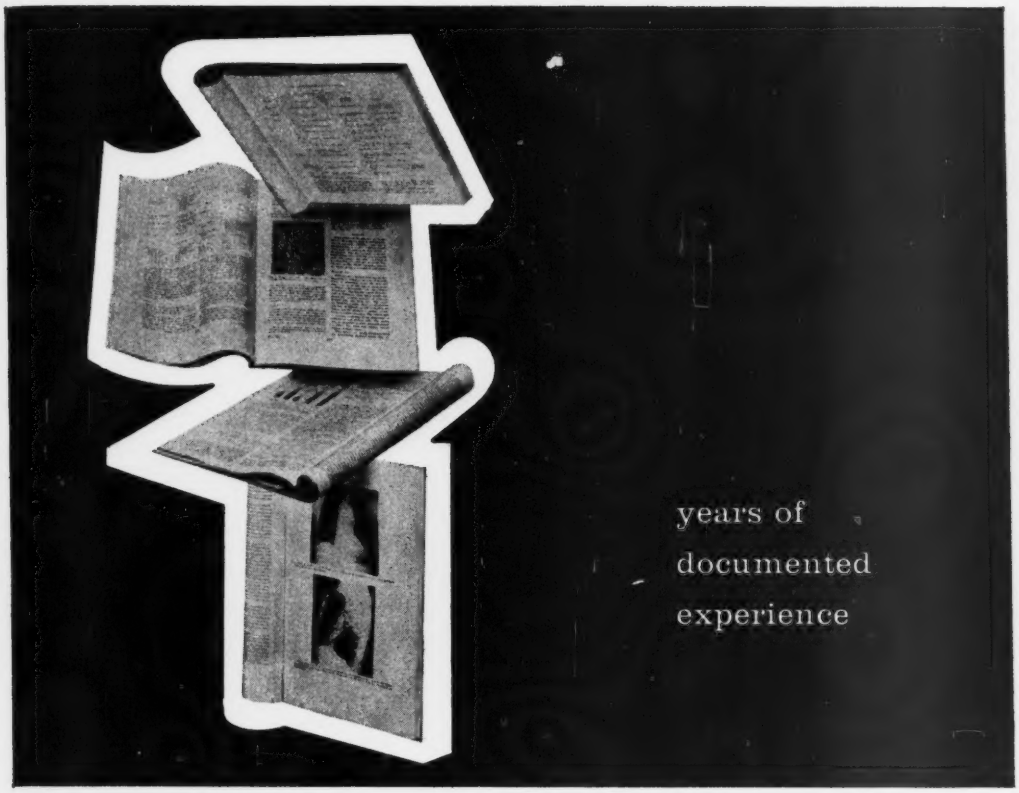
Urokon, intra-arterial, vascular responses to, *472*

Valves
aortic
with mitral stenosis, 930
pressure pulses in, *471*
stenosis. *See* Stenosis, aortic
cinematography of, *784*
commissurotomy. *See* Commissurotomy
dye dilution curves in disorders, *471*
fibroelastic hamartoma of, *141*
mitral
changes of cardiac dynamics in disease, *300*
commissurotomy, 924–932. *See also* Commissurotomy, mitral
duration of diastole in disease, *469*
esophageal balloon tracings in disorders, *788*
experimental studies, *306*
left atrial movements in disorders, *616*
pressure pulse in disease, *470*
pulmonary capillary pressures in, disease, *142*
radiopotassium dilution curves, 532–538
stenosis. *See* Stenosis, mitral
surgery
potassium and cortisone after, *144*
psychiatric complications, *144*
peripheral circulation disorders in disease, *312*

Valves (*Cont'd*)
postcommissurotomy syndrome, 203–209, 269, *787*
pulmonary
absence of, congenital, 397–403
bicuspid, congenital, *296*
stenosis. *See* Stenosis, pulmonary, valvular
in rheumatic fever, *614*
tricuspid
closure in venous pulse in A-V block, *138*
with mitral stenosis, 930
mycotic endocarditis of, *778*
stenosis, *787*, *790*
Valvuloplasty
aortic, 932–934
mitral, 924–932
open, response to, 814–825
Valvulotomy. *See* Commissurotomy
Varicose veins, recurrent, *955*
Vascular conditions
aneurysms. *See* Aneurysms
aorta. *See* Aorta
arteries. *See* Arteries
arteritis, *147*, *148*, 845–849
atherosclerosis. *See* Atherosclerosis
cardiac, *780*
carotid-cavernous fistulas, *618*
chemoreceptors in ear of rabbits, *309*
Chiari syndrome in childhood, *792*
collateral circulation in obstruction of thoracic aorta, *148*
complications in angiography, *146*
in diabetes, *147*
emboli. *See* Emboli
gradual vascular occlusion, *618*
lipomas with ophthalmoplegia, steatorrhea and phlebectasia, *792*
little strokes, *148*
nerve control of joint blood vessels, *793*
pericardial effusion in scleroderma, *955*
peripheral
circulation, *312*, 456
disorders, treatment of, *792*
sympathetic system lesions, *791*
protamine in lipemia, *619*
pulmonary
in congenital cardiac disease, 164–192
in mitral stenosis, 931
in patent ductus arteriosus, *134*
secondary changes, *780*
recurrent varicose veins, *955*
roentgenography of renal arteriovenous fistula, *149*
skin lesions with aging, *619*
thromboangiitis obliterans, *618*
thrombosis. *See* Thrombosis
treatment of Raynaud's syndrome and Buerger's disease, *312*
veins. *See* Veins
Vasoactive drugs, action on oxygen saturation of coronary sinus blood, *300*
Vasodepressor
sympathomimetics, renal vascular response to, *472*
syncope, 875–882
Vasodilator drugs, coronary, symposium, 111–117
Vasomotor responses in neurologic lesions, 518–523
Vasospasm in poliomyelitis, 750
Vectorcardiography, 803, *943*
in bundle-branch block with myocardial infarction, *777*
in diagnosis of congenital malformations, *138*
in left ventricular hypertrophy with conduction delay, *298*
of newborn, *298*
Veins
axillary, occlusion, anticoagulants in, *312*
congestion in rhemogram, *945*
hepatic, thrombosis, *792*
jugular, registration of pulse, *945*
peripheral, diseases in aged, *791*
pulmonary
anomalous connections, surgery in, *617*
drainage anomalies, *610*
surgery in, *954*
obstruction to flow, 191–192
Velocity of blood flow, 448–457
Vena cava
ligation, *953*
thrombosis, *792*
Venomotor tone in venous congestion, *307*
Ventricular conditions
activity studies, 575–590
arrhythmias in heart block, 547–557
conduction disturbances, electrocardiography in, *776*
contraction, and coronary artery pressure, *782*
depolarization, electrical center of, *463*
extrasystoles, coupling intervals of, 82–89
failure
after closure of atrial septal defects, 568–573
pulmonary function in, 492–500
fibrillation. *See* Fibrillation, ventricular
functional single ventricle, 184
hypertrophy
electrocardiography and ventriculography in, *298*
measurements in, *141*
pressure pulses in mitral vavular disease, *470*
repolarization, *944*
septal defect, 172–184, *611*
hydrodynamics in, *461*
with pulmonary stenosis, 182–184
simulating patent ductus arteriosus, *297*
sodium lactate in disorders, 592
standstill, electric pacemaker in, *776*
tachycardia, *301*, 554
Veratrine, tachycardia from, carbon dioxide in, *473*
Veratrum and rauwolfia, effects of mixture, *304*
Vibration analysis of heart sounds and murmurs, *139*
Vitamin E requirements, *947*
Vitamin K_1 in hypoprothrombinemia, *938*
Volumogram and electrogram, relations between, *469*

Warfarin sodium, use of, *939*
Warming, reflex responses to, 518–523
Weight changes in steroid therapy for rheumatic fever, 225–229
Wernicke's encephalopathy, 836–843
Wolff-Parkinson-White syndrome
electrocardiography in, *299*
experimental production of, *136*
Work
heart in, *300*, *302*
return to, after heart disease, *793*, *794*

Xanthomatosis and essential familial hypercholesterolemia, *937*



YOUR PATIENT NEEDS AN ORGANOMERCURIAL

Practicing physicians know that many years of clinical and laboratory experience with any medication are the only real test of its efficacy and safety.

Among available, effective diuretics, the organomercurials have behind them over three decades of successful clinical use. Their clinical background and thousands of reports in the literature testify to the value of the organomercurial diuretics.

TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN (18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA EQUIVALENT TO 10 MG. OF NON-IONIC MERCURY IN EACH TABLET)

LAKESIDE

a standard for initial control of severe failure

MERCUHYDRIN® SODIUM

BRAND OF MERALLURIDE INJECTION

02158

Circulation

JUNE 1957
VOL. XV NO. 6

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

INDEX ISSUE

EDITORIAL

REFLECTIONS ON ELECTROCARDIOGRAPHY ..... *Franklin D. Johnston* 801

SERUM LIPOPROTEIN AND CHOLESTEROL CONCENTRATIONS: COMPARISON OF RURAL COSTA RICAN, GUATEMALAN, AND U. S. POPULATIONS
Nevin S. Scrimshaw, Martha Trulson, Carlos Tejada, D. Mark Hegsted and Fredrick J. Stare 805

VALVULAR PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM: CLINICAL AND PHYSIOLOGIC RESPONSE TO OPEN VALVULOPLASTY
S. Gilbert Blount, Jack van Elk, Oscar J. Balchum and Henry Swan 814

AGING OF ARTERIES IN RELATION TO HYPERTENSION
James Conway and K. Shirley Smith 827

CIRCULATORY STUDIES IN WERNICKE'S ENCEPHALOPATHY: WITH SPECIAL REFERENCE TO THE OCCURRENCE OF A STATE OF HIGH CARDIAC OUTPUT AND POSTURAL HYPOTENSION ..... *Michael A. Gravallese, Jr. and Maurice Victor* 836

OBLITERATIVE BRACHIOCEPHALIC ARTERITIS: PULSELESS DISEASE OF TAKAYASU
Thomas B. Gibbons and Robert L. King 845

THE AUSCULTATORY GAP IN ARTERIOSCLEROTIC HEART DISEASE
Simon Rodbard and Jack Margolis 850

COMPARISON OF MERCURIAL DIURETICS AND BED REST IN NORMAL AND TOXEMIC PREGNANCIES ..... *N. S. Assali, J. Voskian and J. Roller* 855

SIGNIFICANCE OF PULMONARY ELASTIC AND VISCOUS RESISTANCE IN ORTHOPNEA
R. M. Cherniack, T. E. Cuddy and J. B. Armstrong 859

STENOSIS OF A BRANCH OF THE PULMONARY ARTERY: AN ADDITIONAL CAUSE OF CONTINUOUS MURMURS OVER THE CHEST
Frederic Eldridge, Arthur Selzer and Herbert Hultgren 865

VASODEPRESSOR SYNCOPE: FACTORS INFLUENCING CARDIAC OUTPUT
A. M. Weissler, J. V. Warren, E. H. Estes, Jr., H. D. McIntosh and J. J. Leonard 875

ATRIAL DISSOCIATION AND UNIATRIAL FIBRILLATION
George W. Deitz III, Henry J. L. Marriott, Evan Fletcher and Samuel Bellet 883

HEPARIN-ACTIVATED CLEARING FACTOR: STANDARDIZED TEST, AGEWISE APPLICATION, AND CLINICAL OBSERVATIONS ..... *Saul P. Baker* 889

CANCELLATION OF ESOPHAGEAL ELECTROCARDIOGRAMS
Ralph F. Morton, William E. Romans and Daniel A. Brody 897

IDIOPATHIC MYOCARDIAL FAILURE IN THE LAST TRIMESTER OF PREGNANCY AND THE PUERPERIUM ..... *W. R. Meadows* 903

SPECIAL ARTICLE

THE EVOLUTION OF OUR KNOWLEDGE ABOUT THE HEART AND ITS DISEASES SINCE 1628 ..... *Paul D. White* 915

CLINICAL PROGRESS

SELECTION OF PATIENTS FOR MITRAL AND AORTIC VALVULOPLASTY
Laurence B. Ellis, Walter H. Abelmann and Dwight E. Harken 924

ABSTRACTS 936

AMERICAN HEART ASSOCIATION 956

CONTRIBUTORS TO THIS ISSUE 959